Sofosbuvir
For Treatment of Chronic Hepatitis C Infection

Antiviral Drugs Advisory Committee Meeting
Briefing Document

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NDA 204671

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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1. EXECUTIVE OVERVIEW

On 08 April 2013, Gilead Sciences (Gilead) submitted a New Drug Application (NDA) to the United States (US) Food and Drug Administration (FDA) for sofosbuvir (SOF).

SOF is a uridine nucleotide analog with potent anti-viral activity against hepatitis C virus (HCV) genotypes 1 through 6. SOF has a favorable safety profile. When administered in combination with ribavirin (RBV) for genotypes 2 and 3 HCV infection, it is the first all-oral therapy for this patient population, many of whom previously failed treatment or could not be treated. For patients with genotypes 1, 4, 5, and 6 HCV infection, SOF in combination with RBV and pegylated interferon (Peg-IFN) provides a shorter, simpler, and more effective interferon-limiting regimen.

The proposed indication for SOF is for the treatment of chronic HCV infection, in combination with other agents in adult patients with genotype 1 to 6 and/or adult patients awaiting liver transplantation. The recommended dose of SOF is one 400-mg tablet once daily administered orally with or without food. Table 1 summarizes the proposed SOF regimens and treatment durations.

Table 1. Proposed Sofosbuvir Regimens and Treatment Durations

<table>
<tr><th></th><th>Treatment Duration</th><th>SOF Dose</th><th>Peg-IFN Dose</th><th>RBV Dose</th></tr>
<tr><td>Treatment-Naive Patients with Chronic Genotype 1, 4, 5, or 6 HCV Infection</td><td>12 weeks of SOF+Peg-IFN +RBV</td><td rowspan="4">400 mg once daily</td><td>See Peg-IFN prescribing information[a]</td><td>See RBV prescribing information[a, c]</td></tr>
<tr><td>Patients with Chronic Genotype 2 HCV Infection</td><td>12 weeks of SOF+RBV</td><td rowspan="3">N/A</td><td rowspan="3">< 75 kg = 1000 mg/day[b, c]
≥ 75 kg = 1200 mg/day[b, c]</td></tr>
<tr><td>Patients with Chronic Genotype 3 HCV Infection</td><td>16 weeks of SOF+RBV</td></tr>
<tr><td>Patients with Chronic HCV Infection Awaiting Liver Transplantation</td><td>SOF+RBV until liver transplantation</td></tr>
</table>

CL_{cr} = creatine clearance; HCV = hepatitis C virus; N/A = not applicable; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir

a For patients with chronic genotype 5 or 6 HCV infection, refer to the dosing recommendation for patients with chronic genotype 1 or 4 HCV infection.

b The daily dose of RBV is administered orally in 2 divided doses with food.

c Patients with renal impairment ($CL_{cr} \leq 50$ mL/min) require RBV dose reduction; refer to RBV prescribing information.

This document provides background information on SOF for the FDA advisory committee meeting on 25 October 2013. A summary of the data supporting the SOF NDA is presented

in the executive overview. Details on the development of SOF, the SOF clinical program, and the benefit/risk profile are presented in subsequent sections.

1.1. Unmet Medical Need

Chronic HCV infection is a serious, progressive, and potentially life-threatening disease and a major global public health concern. Asymptomatic liver disease progression can occur over several decades {17257}, {25133}. If left untreated, 10% to 40% of these patients are expected to develop cirrhosis and would then be at risk for the development and progression of further complications, including bleeding varices, ascites, hepatic encephalopathy, and hepatocellular carcinoma {13693}, {17257}, {17638}.

An estimated 170 million people are chronically infected with HCV worldwide {24854}. In the US, an estimated 3.2 million people have chronic HCV infection, which will lead to approximately 36,000 deaths each year by 2030 {23407}, {25133}, {10937}, {25895}.

Viral eradication of chronic HCV infection, defined as sustained virologic response (SVR), has been associated with histologic improvement of fibrosis, reduced progression of fibrosis, decreased risk of hepatocellular carcinoma, reduced risk of liver decompensation, and overall reduced all-cause and liver-disease related mortality {6643}, {22614}, {22612}, {22616}. However, current standard-of-care treatments, all of which include interferon, have significant side effects, a long duration of treatment (24 to 48 weeks), and suboptimal response rates {21450}, {24700}, {24701}, {24149}, {25285}, {24932}. As a result there is a large pool of HCV-infected patients—undiagnosed, diagnosed yet untreated, and patients who have failed current therapies—at risk for progression of their liver disease and the attendant morbidity and mortality {21162}.

Since the HCV epidemic began more than three decades ago, a growing proportion of patients have developed cirrhosis and its associated complications, including liver decompensation and liver cancer {17257}. In the US, rates of cirrhosis in patients with chronic HCV infection are projected to be as high as one million patients by 2020 {21162}. Accompanying this increase in cirrhosis, it is also projected that approximately 150,000 and 14,000 patients will develop liver decompensation and liver cancer, respectively {21162}. Because of this burden of advancing disease, chronic HCV infection is now the leading indication for liver transplantation, with approximately 5500 patients awaiting liver transplantation, and this number will continue to increase over future decades {26213}. The aging HCV-infected population, increasing rates of complications, and sequelae of advanced liver disease pose a substantial challenge to health care in the coming decades {23868}. Thus, there is clearly a need for better tolerated and more effective therapies.

1.2. Development Program

Prior to the clinical development of SOF, a comprehensive program of nonclinical studies was conducted to support SOF's favorable benefit/risk profile, including primary and secondary pharmacodynamics; safety pharmacology; absorption, distribution, metabolism, and elimination; and toxicology studies.

The SOF clinical development program includes 13 Phase 1 studies, five Phase 2 studies, four Phase 3 registration studies, one pre-transplant study, and three collaborative studies. More detailed summaries are provided in Table 16 in Section 6.1 for the Phase 2 studies and Table 20 in Section 6.2 for the Phase 3 studies and the Pre-Transplant study.

Overall, 2935 HCV-infected patients received at least one dose of SOF 400 mg in Phase 2 or 3 studies. Of these patients, 2356 received treatment for at least 12 weeks, 818 received treatment for at least 16 weeks, and 709 received treatment for 24 weeks.

1.3. Nonclinical Program

1.3.1. Mechanism of Action

SOF is a uridine nucleotide analog which is active against all genotypes (1 through 6) of the HCV (Section 3.1.1). SOF is a prodrug which delivers the monophosphorylated uridine nucleotide into hepatocytes where two additional phosphate groups are added by intracellular enzymes to form the active triphosphate (2'-deoxy-2'-fluoro-2'-C-methyluridine-triphosphate; GS-461203). SOF exerts its anti-viral activity against the virus by competing with endogenous uridine triphosphate for incorporation into the growing HCV ribonucleic acid (RNA) chain by the nonstructural protein 5B (NS5B) polymerase enzyme. Once incorporated, no further nucleotides can be added and the RNA chain is terminated.

This mechanism of action has a number of advantages which may help explain the efficacy observed in the SOF clinical program. The active site on the NS5B enzyme is well conserved across HCV genotypes because mutations within the active site can potentially affect the enzyme's ability to perform its enzymatic function and may result in a virus which has reduced fitness. This reduced fitness is evident by the lack of detection of the S282T mutation after treatment, which was found to confer resistance to SOF in vitro, in viral isolates from untreated patients, and the lack of viral resistance observed in patients who did not achieve a SVR in the Phase 3 studies. The conservation of the NS5B active site across HCV genotypes preserves the ability of SOF to maintain anti-viral activity across multiple HCV genotypes and subtypes.

1.3.2. In Vitro Anti-viral Activity, Resistance and Cross-resistance Characterization

In vitro, SOF demonstrated potent pan-genotypic activity across the HCV genotypes (1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a) at concentrations of SOF-inhibiting virus replication by 50% (EC_{50} values) of 0.014 to 0.11 µM (Section 3.1.2). When tested against a panel of genotype 1a, 1b, 2b, and 3a clinical HCV isolates, SOF demonstrated similar EC_{50} values to the above laboratory strains of corresponding genotypes. In vitro combination studies showed an additive interaction between SOF and interferon. A minor synergy was observed for the combination of SOF with RBV. No antagonism was observed for any of the combinations tested.

In vitro resistance selections in replicon cells were performed to determine which NS5B mutations might confer resistance to SOF. S282T was the primary mutation selected in all

replicon genotypes tested and site-directed mutagenesis confirmed that S282T conferred reduced susceptibility to SOF; however, the S282T mutation did not confer cross-resistance to other classes of anti-viral inhibitors and appeared to increase sensitivity to RBV in vitro. HCV replicons expressing S282T also showed reduced replication capacity in vitro. Conversely, SOF remained fully active against replicons harboring mutations that conferred resistance to protease inhibitors, nonnucleoside inhibitors, nonstructural protein 5A (NS5A) inhibitors, nucleoside inhibitors (NS5B L159F and L320F), as well as the RBV-associated mutants F415Y and T390I.

1.3.3. Pharmacokinetics and In Vitro Drug Interactions

SOF effectively delivers the nucleoside analog monophosphate to the liver for subsequent conversion to the pharmacologically active triphosphate after oral administration. SOF is almost exclusively eliminated from the body following metabolism to its nucleoside metabolite GS-331007. GS-331007 is the predominant compound observed in plasma after oral administration. Early nonclinical and clinical studies used GS-9851, the diastereomeric mixture containing SOF, which produces the same metabolites as SOF.

SOF is a substrate of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP) and, as such, its intestinal absorption may be affected by inhibitors or inducers of these transporters (Section 3.3). SOF and its predominant metabolite, GS-331007, do not meaningfully interact with traditional hepatic drug metabolism pathways. SOF and its metabolites are not inhibitors, inducers, or meaningful substrates of cytochrome P450 (CYP) enzymes or uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). The intracellular activation of SOF is mediated by low-affinity and high-capacity hydrolase and nucleotide phosphorylation pathways that are not readily inhibited at pharmacologically relevant concentrations achieved by agents that may be co-administered to patients with HCV infection.

Renal elimination of GS-331007 is mediated by a combination of glomerular filtration and active tubular secretion. GS-331007 is not an inhibitor or substrate of transporters that are expressed in the proximal tubule that are known to mediate the active tubular secretion of xenobiotics and that have been implicated in renal drug-drug interactions. Thus, SOF and its metabolites are predicted to have low liability for systemic drug-drug interactions.

1.3.4. Nonclinical Safety Pharmacology and Toxicology

The safety pharmacology and toxicology studies support a favorable benefit/risk profile for SOF (Sections 3.2 and 3.4, respectively).

SOF has shown no significant cytotoxicity in multiple cell lines, including myeloid and erythroid bone marrow progenitor cells. SOF also has a low potential for mitochondrial toxicity, with no significant effects on mitochondrial deoxyribonucleic acid (DNA) levels or mitochondrial transcription or translation in SOF-treated cells, and the triphosphate form of SOF was not an inhibitor of human DNA or RNA polymerases, including mitochondrial polymerases in biochemical studies.

SOF had no clinically relevant effect on the central nervous, cardiovascular, or respiratory systems in safety pharmacology studies. The toxicology profile of SOF is well characterized in multiple animal species. The complete nonclinical program included single-dose oral toxicity study in rats; repeat-dose oral toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), and dogs (up to 39 weeks); genotoxicity tests in vitro and in vivo; a full development and reproductive toxicity program; and 2-year oral carcinogenicity studies in mice and rats which are ongoing.

The nonclinical toxicity studies demonstrate that SOF is generally well tolerated for up to 6 months in the rat and 9 months in the dog with no observed adverse effect levels (NOAELs), providing margins of exposure relative to the exposures in patients treated with the recommended clinical dose (400 mg) of 9-fold (rat) and 13-fold (dog) for GS-331007. SOF is considered non-genotoxic. No adverse effects on fertility, embryo-fetal development, or pre- and post-natal development were observed, and the NOAELs were ≥ 10-fold relative to the mean clinical exposure at SOF 400 mg. SOF was negative for delayed-type hypersensitivity and was not considered a skin or eye irritant.

1.4. Clinical Development Program

The SOF clinical development program included 13 Phase 1 studies, five Phase 2 studies, four Phase 3 registration studies, one pre-transplant study, and three collaborative studies (Section 4). The Phase 2 and 3 studies evaluated SOF in combination with RBV with or without Peg-IFN for treatment in the most common HCV genotypes (1 through 6). A unique feature of the SOF program was the number of patient populations studied. A significant proportion of the patients included in the SOF clinical studies would have been excluded from participation in interferon-containing regimens, such as patients with advanced age, patients with higher body mass index (BMI), patients receiving opiate replacement therapy, a significant proportion of patients with advanced liver disease or cirrhosis, and patients with relative or absolute contraindications to interferon.

There are ongoing studies with SOF+RBV treatment, including studies in special HCV populations such as patients awaiting liver transplantation. Three collaborative studies have also been conducted or are ongoing: the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored SPARE study with SOF and RBV, Bristol-Myers Squibb (BMS)-sponsored Study A1444040 with SOF and daclatasvir (DCV) with and without RBV, and Janssen Pharmaceuticals, Inc. (Janssen) Study HPC2002 with SOF and simeprevir (SMV) with and without RBV.

1.4.1. Clinical Pharmacology

SOF exhibits a favorable clinical pharmacology profile. GS-331007 is the primary circulating metabolite in humans and is considered to be the primary analyte of interest in clinical pharmacology studies.

The following key results were demonstrated in the SOF clinical pharmacology program:

- Single- and multiple-dose pharmacokinetic (PK) studies showed that SOF was absorbed quickly following oral administration and exhibited approximately linear PK, regardless of dose level administered in patients with HCV infection and in healthy subjects. SOF, a nucleotide analog prodrug, undergoes metabolism intrahepatically to form the long-lived active nucleoside triphosphate analog, GS-461203. In nonclinical studies, GS-461203 exhibited a long intrahepatic $t_{1/2}$ (17.8 hours in dogs) that makes SOF suitable for once-daily administration (Sections 5.2.4 and 5.2.5).

- Dose-ranging studies conducted as either monotherapy or combination therapy with Peg-IFN+RBV revealed exposure response relationships that supported the dose selection of SOF 400 mg once daily for the treatment of chronic HCV infection (Section 5.3.1).

- A human mass balance study showed that renal excretion was the primary route of elimination for the SOF metabolite GS-331007 (Section 5.2.3).

- A thorough QTc study demonstrated SOF at therapeutic and supratherapeutic doses had no effect on the QTcF interval in humans (Section 5.3.3).

- A food effect study showed no clinically significant effect of food. Dosing of SOF in Phase 2 and 3 clinical studies was recommended without regard to food; however, in all of the Phase 3 studies, SOF was coadministered with RBV, which is dosed with food per RBV prescribing information (Section 5.2.1) {21450}.

- Studies in patients with varying degrees of renal function and hepatic impairment indicated that no dose adjustment of SOF is needed for patients with mild to moderate renal impairment or patients with mild, moderate, or severe hepatic impairment (Sections 5.2.8 and 5.2.9, respectively).

- Drug-drug interaction studies showed that, in agreement with in vitro data, there were no clinically significant drug-drug interactions between SOF and cyclosporin A, tacrolimus, methadone, or the HIV anti-retrovirals (ARVs) efavirenz, emtricitabine, tenofovir disoproxil fumarate, darunavir, ritonavir, raltegravir, or rilpivirine (Sections 5.2.10.1 and 5.2.10.2). Coadministration of SOF 400 mg with zidovudine, lamivudine, and atazanavir is permitted in an ongoing study in HCV/HIV-co-infected patients.

- SOF is a substrate of drug transporter Pgp and BCRP, but GS-331007 is not. Drugs that are potent Pgp inducers in the intestine may significantly decrease SOF plasma concentration leading to reduced therapeutic effect of SOF (eg, rifampin or St John's Wort) and should not be used with SOF {23953}, {11178}, {23954}, {23955} (Sections 5.2.10 and 5.2.11).

1.5. Efficacy in Phase 2 Studies

The results of the Phase 2 studies supported the following conclusions and formed the basis for the design of the Phase 3 registration studies (Section 6.1):

- Confirmed SOF's potent and rapid suppression of HCV RNA against HCV genotypes 1, 2, 3, 4, and 6
- Established 400 mg once daily as the efficacious dose for SOF (Section 6.1.1)
- Showed that HCV genotypes 2 and 3 can be effectively treated with SOF+RBV with and without Peg-IFN (Section 6.1.2)
- Showed the addition of Peg-IFN to SOF+RBV treatment increases the response rate for HCV genotypes 1, 4, and 6 and allows the duration of therapy to be decreased to 12 weeks (Section 6.1.3)
- Showed that SOF used in combination with RBV with and without Peg-IFN was generally safe and well tolerated

1.6. Efficacy in Phase 3 Studies

The Phase 3 program was composed of four registration studies: three studies in HCV genotypes 2 and 3 and one study in HCV genotypes 1, 4, 5, and 6 (Section 6.2).

The studies in patients with genotype 2 or 3 HCV infection are unique in that each study evaluated a different patient population:

- **Treatment-naive patients (FISSION [Study P7977-1231]):** Patients who had not been previously treated for chronic HCV infection. For this patient population, the currently recommended treatment is Peg-IFN+RBV for 24 weeks {13693}.
- **Patients who were interferon intolerant, ineligible, or unwilling to take interferon option (POSITRON [GS-US-334-0107]):** This patient population currently has no treatment.
- **Treatment-experienced patients (FUSION [Study GS-US-334-0108]):** Patients who had previously failed Peg-IFN or interferon plus RBV treatment. The American Association for the Study of Liver Diseases (AASLD) treatment guidelines do not recommend re-treatment for patients who have failed a course of Peg-IFN+RBV; however, these patients can be re-treated with Peg-IFN+RBV for 48 weeks based on the Peg-IFN+RBV prescribing information {13693}, {24701}.

In addition, the NEUTRINO study (Study GS-US-334-0110) was conducted in patients with genotype 1, 4, 5, or 6 HCV infection and included interferon-eligible patients. For genotype 1 HCV infection, the currently recommended treatment is a protease inhibitor in combination with Peg-IFN+RBV for 24 to 48 weeks {19759}. For genotype 4 or 6 HCV infection, the

currently recommended treatment is Peg-IFN+RBV, and for genotype 5 HCV infection, there is no currently recommended treatment {13693}.

Table 2 presents the study design and primary results for the four Phase 3 registration studies—FISSION, POSITRON, FUSION, and NEUTRINO.

Table 2. Overview of Phase 3 Clinical Studies in the Sofosbuvir Clinical Program

Study	Treatment Regimens[a]	N[b]	SVR12 %	Primary Result[a]
Studies in Patients with Genotype 2 or 3 HCV Infection				
FISSION (Treatment-naive)	SOF+RBV 12 weeks Peg-IFN+RBV 24 weeks	253 243	67% 67%	Noninferiority demonstrated (SOF+RBV vs Peg-IFN+RBV; p< 0.001)
POSITRON (Intolerant, ineligible, or unwilling to take interferon)	SOF+RBV 12 weeks placebo 12 weeks	207 71	78% 0%	Superiority demonstrated (SOF+RBV vs placebo; p< 0.001)
FUSION (Treatment-experienced)	SOF+RBV 12 weeks SOF+RBV 16 weeks	100 95	50% 73%	Superiority demonstrated against 25% historical rate (SOF+RBV 12 Weeks and 16 Weeks; p< 0.001)
Studies in Patients with Genotype 1, 4, 5, or 6 HCV Infection				
NEUTRINO (Treatment-naive)	SOF+Peg-IFN+RBV 12 weeks	327	90%	Superiority demonstrated to 60% historical rate (SOF+Peg-IFN+RBV; p< 0.001)

HCV = hepatitis C virus; LLOQ = lower limit of quantitation; Peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug; vs = versus

Note: In the FISSION, POSITRON, and FUSION studies, 20%, 16%, and 34% of patients had cirrhosis, respectively. In the NEUTRINO study, 17% of patients had cirrhosis.

Note: The primary efficacy endpoint was SVR12, which was defined as HCV RNA < LLOQ 12 weeks after cessation of study drug.

a All Phase 3 registration studies met their primary objective.

b Patients in full analysis set (defined as patients with the protocol-specified HCV genotypes who were randomized and received at least one dose of study drug)

The study designs, statistical considerations, and individual study results of the four Phase 3 studies—FISSION, POSITRON, FUSION, and NEUTRINO—are described in the following sections. All studies had the same primary endpoint: SVR12, defined as HCV RNA result below the lower limit of quantification (LLOQ; < 25 IU/mL) using the Cobas Taqman Assay Version 2.0 for use with the High Pure System at 12 weeks after the end of treatment.

1.6.1. Primary Efficacy Endpoint for the Phase 3 Studies

In the four Phase 3 studies, the intent-to-treat analysis set was defined as the group of patients who received at least one dose of study drug. The full analysis set was defined as the group of patients with the protocol-specified HCV genotypes who were randomized and

received at least one dose of study drug. For the POSITRON and NEUTRINO studies, the intent-to-treat and full analysis sets were identical. However, in the FISSION and FUSION studies, the genotypes of nine patients were misclassified: three patients each in the SOF+RBV group in the FISSION study, SOF+RBV 12 Week group in the FUSION study, and SOF+RBV 16 Week group in the FUSION study. These patients were determined to have genotype 2 HCV infection at screening using by the VERSANT® HCV Genotype INNO-LiPA 2.0 (LiPA) screening assay (n = 8) or the Abbott RealTime HCV Genotype II assay (n = 1), but shown to have genotype 1 HCV infection by NS5B sequencing assay. Eight of these nine patients were shown to have genotype 2 HCV core protein upon further HCV core sequencing. Therefore, these eight patients were infected with recombinant genotype 1/2 HCV with the core from genotype 2 HCV and NS5B from genotype 1 HCV. The remaining patient was determined to have genotype 2 HCV infection at screening, but shown to have genotype 1 HCV infection by NS5B sequencing, with HCV core sequencing analysis ongoing. As a result, these nine patients were excluded from the full analysis set as was pre-specified in the statistical analysis plan.

Table 3 presents the primary efficacy endpoint, SVR12, for the intent-to-treat analysis set and full analysis set in the FISSION, POSITRON, FUSION, and NEUTRINO studies.

Table 3. FISSION, POSITRON, FUSION, and NEUTRINO: SVR12 for Intent-To-Treat and Full Analysis Sets

Study	Treatment		Intent-To-Treat Analysis Set	Full Analysis Set
FISSION	SOF+RBV 12 Weeks	SVR, n/N (%)	171/256 (67%)	170/253 (67%)[a]
		95% CI	61% to 73%	61% to 73%
	Peg-IFN+RBV 24 Weeks	SVR, n/N (%)	162/243 (67%)	162/243 (67%)
		95% CI	60% to 73%	60% to 73%
POSITRON[b]	SOF+RBV 12 Weeks	SVR, n/N (%)	161/207 (78%)	161/207 (78%)
		95% CI	71% to 83%	71% to 83%
FUSION	SOF+RBV 12 Weeks	SVR, n/N (%)	51/103 (50%)	50/100 (50%)[c]
		95% CI	40% to 60%	40% to 60%
	SOF+RBV 16 Weeks	SVR, n/N (%)	70/98 (71%)	69/95 (73%)[c]
		95% CI	61% to 80%	63% to 81%
NEUTRINO	SOF+Peg-IFN +RBV 12 Weeks	SVR, n/N (%)	295/327 (90%)	295/327 (90%)
		95% CI	86% to 93%	86% to 93%

Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug

a In the FISSION study, three patients in the SOF+RBV group were determined to have genotype 2 HCV infection at screening. Two patients were shown to have recombinant genotype 1/2 HCV infection upon further sequencing, and one patient was shown to have genotype 1 HCV infection by NS5B sequencing, with further HCV core sequencing ongoing. These three patients were excluded from analyses for the full analysis set.

b None of the patients in the placebo group in the POSITRON study achieved SVR12 and results for the placebo group are not included in this table.

c In the FUSION study, three patients each in the SOF+RBV 12 Week and 16 Week groups were determined to have genotype 2 HCV infection at screening, but were shown to have recombinant genotype 1/2 HCV infection upon further sequencing and were excluded from analyses for the full analysis set.

The SVR rates were similar between the intent-to-treat analysis set and full analysis set in each of the four studies and did not change the interpretations. Therefore, unless otherwise specified, the efficacy results for the four Phase 3 studies are presented for the full analysis set in the following sections.

1.6.2. FISSION: Treatment-Naive Patients with Chronic Genotype 2 or 3 HCV Infection

FISSION, a randomized, open-label, active-controlled study, evaluated the efficacy and safety of SOF+RBV treatment for 12 weeks compared with Peg-IFN+RBV treatment for 24 weeks in treatment-naive patients with chronic genotype 2 or 3 HCV infection (Section 6.2.5.1). Patients were equally randomized to receive either SOF+RBV for 12 weeks or Peg-IFN+RBV for 24 weeks in a prespecified 3:1 ratio of patients with genotype 2 or genotype 3 HCV infection. Treatment with Peg-IFN+RBV for 24 weeks was selected as the control in this study because it is the recommended treatment for this patient population.

Noninferiority was tested for the difference in SVR12 rates of SOF+RBV and Peg-IFN+RBV treatment based on stratum-adjusted Mantel-Haenszel proportions. The noninferiority margin of 15% was used for SVR12 based on the clinical assessment that eliminating Peg-IFN from the treatment regimen and shortening the duration of treatment from 24 to 12 weeks would result in a substantial benefit to the patient.

Table 4 presents the proportion of patients with SVR12 overall and by genotype and cirrhosis status. The primary efficacy endpoint of noninferiority was met for SOF+RBV treatment for 12 weeks compared with Peg-IFN+RBV treatment for 24 weeks, with 67% of patients achieving SVR12 in both treatment groups. In both treatment groups, patients with genotype 2 HCV infection had higher SVR12 rates than patients with genotype 3 HCV infection. Non-cirrhotic patients also had higher SVR12 rates than cirrhotic patients in both treatment groups. For the SOF+RBV group, a multivariate logistic regression analysis showed that HCV genotype 2 ($p < 0.001$) and the absence of cirrhosis ($p = 0.005$) were strongly associated with a higher SVR rate.

Table 4. FISSION: SVR12 by Genotype and Cirrhosis Status

Treatment	Cirrhosis Status	FISSION SVR12 Genotype 2/3 n/N (%)	FISSION SVR12 Genotype 2 n/N (%)	FISSION SVR12 Genotype 3 n/N (%)
SOF+RBV 12 Weeks	Overall	170/253 (67%)[a]	68/70 (97%)	102/183 (56%)
	No Cirrhosis	147/204 (72%)	58/59 (98%)	89/145 (61%)
	Cirrhosis	23/49 (47%)	10/11 (91%)	13/38 (34%)
Peg-IFN+RBV 24 Weeks	Overall	162/243 (67%) [a]	52/67 (78%)	110/176 (63%)
	No Cirrhosis	143/193 (74%)	44/54 (81%)	99/139 (71%)
	Cirrhosis	19/50 (38%)	8/13 (62%)	11/37 (30%)

CI = confidence interval; HCV = hepatitis C virus; Peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug
Note: Three patients in the SOF+RBV group were determined to have genotype 2 HCV infection at screening. Two patients were shown to have recombinant genotype 1/2 HCV infection upon further sequencing, and one patient was shown to have genotype 1 HCV infection by NS5B sequencing, with HCV core sequencing ongoing. These three patients were excluded from analyses for the full analysis set.

a The stratum-adjusted difference in the proportions was 0.3% [95% CI: –7.5% to 8.0%]; the lower bound of the 2-sided 95% CI on the difference in SVR12 rates [ie, SOF+RBV group − Peg-IFN+RBV group] was > –15%. Superiority of SOF+RBV over Peg-IFN+RBV was not demonstrated (p = 0.94, Cochran-Mantel-Haenszel test stratified by HCV genotype, screening HCV RNA, and cirrhosis status).

1.6.3. POSITRON: Patients with Chronic Genotype 2 or 3 HCV Infection who were Interferon Intolerant, Ineligible, or Unwilling

POSITRON, a randomized, double-blind, placebo-controlled study, evaluated the efficacy and safety of SOF+RBV treatment compared with a matched placebo control for 12 weeks in patients with chronic genotype 2 or 3 HCV infection who were interferon intolerant,

ineligible (medical conditions precluding interferon therapy), or unwilling (Section 6.2.5.2). Similar proportions of patients with genotype 2 and 3 HCV infection were enrolled (51% and 49%, respectively). Patients were randomized in a 3:1 ratio to receive either SOF+RBV or placebo. The placebo control group in this study was selected because there is no current treatment available for HCV-infected patients who are interferon intolerant, interferon ineligible, or unwilling to receive treatment with interferon. This study also provided an opportunity to assess the safety profile of SOF+RBV treatment compared with a placebo control. The difference in SVR12 rates between treatment groups was assessed for superiority. Superiority would be demonstrated if the p-value from a 2-sided Cochran-Mantel-Haenszel test associated with the test of superiority was < 0.05.

Table 5 presents the proportion of patients with SVR12 overall and by genotype and cirrhosis status. A statistically significant higher proportion of patients achieved SVR12 following SOF+RBV treatment for 12 weeks compared with placebo ($p < 0.001$). The primary objective of superiority of SOF+RBV treatment over placebo was met. Patients with genotype 2 HCV infection had a higher SVR12 rate than patients with genotype 3 HCV infection. Non-cirrhotic patients also had a higher SVR12 rate than cirrhotic patients. The difference in SVR12 rate in cirrhotic patients was attributable to differences between cirrhotic and non-cirrhotic patients with genotype 3 HCV infection; cirrhotic and non-cirrhotic patients with genotype 2 HCV infection had similarly high rates of SVR12. For the SOF+RBV group, a multivariate logistic regression analysis showed that HCV genotype 2 was significantly associated with higher SVR rates ($p < 0.001$).

Table 5. POSITRON: SVR12 by Genotype and Cirrhosis Status

		POSITRON		
		SVR12		
Treatment	**Cirrhosis Status**	**Genotype 2/3 n/N (%)**	**Genotype 2 n/N (%)**	**Genotype 3 n/N (%)**
SOF+RBV 12 Weeks	Overall	161/207 (78%)[a]	101/109 (93%)	60/98 (61%)
	No Cirrhosis	142/176 (81%)	85/92 (92%)	57/84 (68%)
	Cirrhosis	19/31 (61%)	16/17 (94%)	3/14 (21%)
Placebo	Overall	0/71	0/34	0/37
	No Cirrhosis	0/58	N/A	N/A
	Cirrhosis	0/13	N/A	N/A

CI = confidence interval; HCV = hepatitis C virus; N/A = not available; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug

a The primary efficacy endpoint of superiority was met for 12 weeks of SOF+RBV compared with placebo, with 78% (95% CI: 71% to 83%) of patients with genotype 2 or 3 HCV infection achieving SVR12 in the SOF+RBV treatment group versus 0% (95% CI: 0% to 5%) in the placebo group ($p < 0.001$).

1.6.4. FUSION: Treatment-Experienced Patients with Chronic Genotype 2 or 3 HCV Infection

FUSION, a randomized, double-blind study, evaluated the efficacy and safety of SOF+RBV treatment for 12 or 16 weeks in treatment-experienced patients with chronic genotype 2 or 3 HCV infection (Section 6.2.5.3). The treatment-experienced genotype 2 or 3 population was selected for this study because of the lack of treatment options available for this patient population. The current treatment guidelines recommend that patients who did not achieve an SVR after a complete course of Peg-IFN+RBV treatment should be not retreated {13693}. A 16-week duration of SOF+RBV treatment was selected to determine if a longer treatment duration improved the response rate. The 2 primary statistical hypotheses of this study were the SVR12 rates in both treatment groups were higher than a null rate of 25% based on SVR rates from the EPIC study for patients with genotype 2 or 3 HCV infection and an expected improved safety profile and shorter duration of treatment {17114}. Both hypotheses were tested at a significance level of 0.025 using a Bonferroni correction to adjust for multiple testing.

Table 6 presents the proportion of patients with SVR12 overall and by genotype and cirrhosis status. The primary efficacy endpoint of superiority was met with both 12 and 16 weeks of SOF+RBV treatment compared with a historic control SVR12 rate of 25% ($p < 0.001$ for both treatment groups). Treatment with 16 weeks of SOF+RBV resulted in higher SVR12 rates compared with the shorter treatment duration of 12 weeks ($p < 0.001$). For both treatment groups, a multivariate logistic regression analysis showed that HCV genotype 2 was significantly associated with a higher SVR rate ($p < 0.001$ and $p = 0.003$ for the SOF+RBV 12 Week and 16 Week groups, respectively).

For both genotypes 2 and 3 HCV infection, the presence of cirrhosis had an effect on the SVR rates, with lower SVR rates for cirrhotic patients in both treatment durations compared with non-cirrhotic patients. In cirrhotic patients, the duration of therapy of SOF+RBV had a substantial influence on SVR in patients with genotype 3 HCV infection, but had a smaller effect on patients with genotype 2 HCV infection. In cirrhotic patients with genotype 2 HCV infection, the SVR12 rates with 12 and 16 weeks of treatment were 60% and 78%, respectively, whereas cirrhotic patients with genotype 3 HCV infection had substantially higher SVR12 rates with 16 weeks (61%) compared with 12 weeks (19%).

Table 6. FUSION: SVR12 Overall and by Genotype and Cirrhosis Status

Treatment	Cirrhosis Status	FUSION SVR12 Genotype 2/3 n/N (%)	FUSION SVR12 Genotype 2 n/N (%)	FUSION SVR12 Genotype 3 n/N (%)
SOF+RBV 12 Weeks	Overall	50/100 (50%)[a]	31/36 (86%)	19/64 (30%)
	No Cirrhosis	39/64 (61%)	25/26 (96%)	14/38 (37%)
	Cirrhosis	11/36 (31%)	6/10 (60%)	5/26 (19%)
SOF+RBV 16 Weeks	Overall	69/95 (73%)[a]	30/32 (94%)	39/63 (62%)
	No Cirrhosis	48/63 (76%)	23/23 (100%)	25/40 (63%)
	Cirrhosis	21/32 (66%)	7/9 (78%)	14/23 (61%)

HCV = hepatitis C virus; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug
Note: Three patients each in the SOF+RBV 12 Week and 16 Week groups were determined to have genotype 2 HCV infection at screening, but were shown to have recombinant genotype 1/2 HCV infection upon further sequencing and excluded from this analysis.

a The primary efficacy endpoint of superiority was met in patients with genotype 2 or 3 HCV infection with 12 and 16 weeks of SOF+RBV treatment compared with an historic control SVR12 rate of 25%, with 50% and 73% of patients achieving SVR12, respectively ($p < 0.001$ for both).

1.6.5. NEUTRINO: Treatment-Naive Patients with Chronic Genotype 1, 4, 5, or 6 HCV Infection

NEUTRINO, a single-group, open-label study evaluated the efficacy and safety of SOF+Peg-IFN+RBV treatment for 12 weeks in treatment-naive patients with chronic genotype 1, 4, 5, or 6 HCV infection (Section 6.2.6.1). The primary efficacy analysis assessed whether patients who received SOF+Peg-IFN+RBV for 12 weeks achieved an SVR12 rate greater than the historical control rate of 60%. The 60% SVR null rate was derived from Phase 3 telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data and accounted for the higher number of cirrhotic patients in the NEUTRINO study, the improved safety profile, and shorter treatment duration {17996}, {17492}, {25285}, {24932}. Superiority would be established if the p-value from a two-sided one-sample exact test was < 0.05.

Table 7 presents the proportion of patients with SVR12 overall and by genotype. The primary objective of superiority of 12 weeks of SOF+Peg-IFN+RBV treatment compared with a predefined historic control SVR12 rate of 60% was met, with 90% of patients achieving SVR12 ($p < 0.001$). Rates of SVR12 did not differ greatly by HCV genotype: 89% for patients with genotype 1 HCV infection and 97% for patients with genotype 4, 5, or 6 HCV infection. Subgroup analyses demonstrated that all subgroups had high SVR rates ($\geq 80\%$). A multivariate logistic regression analysis showed the IL28B non-CC genotypes ($p = 0.006$) and cirrhosis ($p = 0.002$) were strongly associated with lower SVR rates.

Table 7. NEUTRINO: SVR12 Overall and by Genotype

	NEUTRINO
	SOF+Peg-IFN+RBV 12 Weeks
	N = 327 n/N (%)
SVR	295/327 (90%)[a]
Genotype	
1 (1a, 1b, 1a/1b)	261/292 (89%)
4	27/28 (96%)
5	1/1 (100%)
6	6/6 (100%)

CI = confidence interval; HCV = hepatitis C virus; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR= sustained virologic response

a Compared with a predefined historic control SVR rate of 60%, with 90% of patients with genotype 1, 4, 5, or 6 HCV infection achieving SVR12 after completing therapy (95% CI: 86% to 93%, $p < 0.001$).

1.6.6. Resistance Surveillance in Patients who did not Achieve SVR

Across the four Phase 3 registration studies, no genotypic or phenotypic viral resistance to SOF or RBV was detected (Section 6.3). Only one on-treatment virologic failure (breakthrough), potentially due to noncompliance, was observed in patients receiving a SOF-based regimen in the four Phase 3 registration studies. Resistance analyses were attempted on plasma HCV isolates from all patients who had HCV RNA > 1000 IU/mL and an available plasma sample at the time of virologic failure or early discontinuation.

Among patients receiving SOF in the Phase 2 and 3 studies, 302 of 1662 patients qualified to be part of the resistance analysis population and, of these patients, 300 had NS5B sequences available. The S282T substitution was only detected in 1 of the 300 patients with deep sequencing data available for 294 of 300 patients; this patient had received SOF monotherapy and was successfully re-treated with SOF+RBV.

1.6.7. Efficacy Conclusions and Proposed Treatment Recommendations

1.6.7.1. Genotype 2 or 3 Infection

The current standard-of-care for treatment-naive patients infected with genotype 2 or 3 HCV infection is Peg-IFN+RBV for 24 weeks. The AASLD treatment guidelines do not recommend re-treatment for patients who have failed a course of Peg-IFN+RBV; however, these patients can be re-treated with Peg-IFN+RBV for 48 weeks based on the Peg-IFN+RBV prescribing information {13693}, {24701}. Patients who are medically ineligible, intolerant, or unwilling to receive interferon treatment have no treatment option.

In the Phase 3 SOF clinical program, patients with genotype 2 or 3 HCV infection were studied together based on the Phase 2 data in which the SVRs with SOF-containing regimens were similar. However, when SVR12 data from the Phase 3 studies and a multivariate

logistic regression analysis showing that the only consistent factor associated with response was HCV genotype are considered, it is clear that treatment responses can differ substantially between HCV genotypes 2 and 3 with SOF-containing regimens; therefore, it is appropriate to summarize the results separately.

1.6.7.2. Genotype 2 HCV Infection

For patients with genotype 2 HCV infection, the overall SVR12 rates for SOF+RBV treatment for 12 weeks were high across the Phase 3 studies. The SVR12 rates ranged from 86% in treatment-experienced patients receiving SOF+RBV for 12 weeks to 97% in treatment-naive patients receiving SOF+RBV for 12 weeks compared with the SVR12 rate of 78% for treatment-naive patients who received Peg-IFN+RBV for 24 weeks. Thus, the proposed recommended treatment for all patients with genotype 2 HCV infection is SOF+RBV for 12 weeks.

1.6.7.3. Genotype 3 HCV Infection

In contrast to the Phase 2 data, both treatment-naive and treatment-experienced patients with genotype 3 HCV infection had lower SVR rates than those patients with genotype 2 HCV infection. In addition, treatment-experienced patients had lower SVR rates than treatment-naive patients when treated for 12 weeks; however, this difference was mitigated when treatment duration was extended to 16 weeks.

Treatment-naive patients with genotype 3 HCV infection in the FISSION and POSITRON studies who received SOF+RBV for 12 weeks had similar SVR rates (56% and 61%, respectively), which were also similar to patients who received Peg-IFN+RBV for 24 weeks (63% in the FISSION study). In contrast, treatment-experienced patients with genotype 3 HCV infection in the FUSION study who received SOF+RBV for 12 weeks had substantially lower SVR rates (30%) than treatment-naive patients in the POSITRON study who were treated for the same duration. However, when the treatment duration was extended from 12 to 16 weeks in the FUSION study, the SVR rate (62%) was similar to that achieved in treatment-naive patients. Since treatment-naive patient populations include a subgroup of patients that would be treatment failures if treated with Peg-IFN+RBV, it is reasonable to assume that 16 weeks of treatment will also increase the response rate in treatment-naive patients.

In order to quantify the potential improvement in SVR rates that might be observed with a 16-week regimen in treatment-naive patients with genotype 3 HCV infection, a bridging analysis using a logistic regression model was performed. A logistic regression model was fitted to combined SVR12 data from the FISSION and FUSION studies and assessed the impact of treatment duration while controlling for sex, baseline HCV RNA, and cirrhosis status. Based on the logistic regression model, the predicted SVR12 rate for treatment-naive patients following 16 weeks of SOF+RBV treatment would reach 78% if the full benefit observed from extending treatment duration from 12 to 16 weeks in the FUSION study is preserved. In addition, results of these bridging analyses indicate that for cirrhotic and non-cirrhotic treatment-naive patients with genotype 3 HCV infection increasing the SOF+RBV treatment duration from 12 to 16 weeks may increase the SVR12 rate to 76% and 79%, respectively.

Based on the available data in the treatment-experienced patients with genotype 3 HCV infection and the results of the bridging analysis, the proposed recommended treatment for all patients with genotype 3 HCV infection is SOF+RBV for 16 weeks.

An ongoing study is prospectively evaluating 16- and 24-week SOF+RBV treatment regimens in patients with genotype 3 HCV infection (treatment-naive and treatment-experienced patients with and without cirrhosis) (Appendix 1).

1.6.7.4. Genotype 1, 4, 5, or 6 HCV Infection

The current standard-of-care for treatment-naive patients with genotype 1 HCV infection is a protease inhibitor for varying durations in combination with Peg-IFN+RBV for a total duration of 24 or 48 weeks {19759}, {25285}, {24932}. Limitations of this treatment include poor tolerability, numerous drug-drug interactions, a high pill burden and dosing frequency, complex response-guided treatment algorithms, long-treatment duration, and a low genetic barrier to resistance that is associated with virologic breakthrough and virologic resistance in most patients who fail these regimens. The currently recommended treatment for patients with chronic genotype 4 or 6 HCV infection is Peg-IFN+RBV for 48 weeks; there is no recommended treatment for patients with chronic genotype 5 HCV infection {13693}.

In the NEUTRINO study, a statistically significant higher proportion of patients who received SOF+Peg-IFN+RBV for 12 weeks achieved SVR12 (90%) compared with a historical SVR12 rate of 60%. The NEUTRINO study confirmed the results of SOF+Peg-IFN+RBV treatment for 12 weeks in the Phase 2 ATOMIC study (SVR rates of 90% each) which are higher than those achieved with any currently available HCV treatment {25285}, {24932}.

Among the 35 patients with genotype 4, 5, or 6 HCV infection, 34 achieved SVR12 (1 patient with genotype 4 HCV infection with cirrhosis did not achieve SVR12). These results compare favorably with current standard-of-care therapy, Peg-IFN+RBV for 48 weeks, which have reported SVR results in the range of 50% to 80% for genotypes 4, 5, and 6 HCV infection {4481}, {22111}, {22602}, {22603}, {22604}, {22605}.

Of note, a high level of efficacy was demonstrated in the NEUTRINO study for all subgroups of patients (eg, genotype, cirrhosis status, IL28B genotype, baseline HCV RNA, age, sex, race, ethnicity, baseline BMI) with ≥ 80% of patients achieving SVR12 including those with cirrhosis.

The proposed recommended treatment for treatment-naive patients with genotype 1, 4, 5, or 6 HCV infection is SOF+Peg-IFN+RBV for 12 weeks.

1.7. Safety

The primary safety population is composed of patients from the four Phase 3 registration studies and includes patients with genotype 2 or 3 HCV infection receiving SOF+RBV for 12 or 16 weeks, placebo for 12 weeks, or Peg-IFN+RBV for 24 weeks and patients with genotype 1, 4, 5, or 6 HCV infection receiving SOF+Peg-IFN+RBV for 12 weeks

(Section 7). The safety data from the Phase 2 studies support and are consistent with the safety profile observed in the primary safety population of the Phase 3 registration studies.

The three Phase 3 registration studies of SOF+RBV in patients with genotype 2 or 3 HCV infection assessed the safety profile of SOF+RBV treatment as compared with Peg-IFN+RBV treatment (FISSION) and placebo treatment (POSITRON). The safety profile of SOF+RBV treatment for 12 or 16 weeks (FUSION) was also evaluated. These safety analyses included the 566 patients who received SOF+RBV for 12 weeks by individual study and pooled from the 12-week treatment groups in the FISSION, POSITRON, and FUSION studies; 98 patients who received SOF+RBV for 16 weeks in the FUSION study; 71 patients who received placebo in the POSITRON study; and 243 patients who received Peg-IFN+RBV for 24 weeks in the FISSION study. Through the time of the 90-day safety update, an additional 165 patients had received SOF+RBV treatment for 24 weeks in the Phase 2 QUANTUM study and a Phase 2 study in Egyptian patients with genotype 4 HCV infection.

In addition, safety analyses include the 327 patients who received SOF+Peg-IFN+RBV for 12 weeks in the NEUTRINO study. Available data are also provided on the safety of SOF+RBV treatment for 61 patients awaiting liver transplantation.

In the SOF clinical development program, patients were assessed for adverse events (AEs) and laboratory evaluations on a pre-specified schedule. All AEs and laboratory abnormalities discussed in this overview were treatment emergent (defined as from first dose of study drug through 30 days after the last dose of study drug). All patients who received at least one dose of any study drug are included in the safety analyses set.

1.7.1. Safety of SOF+RBV Treatment in Patients with Genotype 2 or 3 HCV Infection

In the FISSION, POSITRON, and FUSION studies, completion of study treatment was high, with 96% to 100% of patients in the SOF-containing or placebo groups completing treatment; the Peg-IFN+RBV group had the lowest rate with 78% of patients completing treatment (Section 7.1, Table 39). This difference in the rates of completion of study treatment was predominantly driven by the higher rates of discontinuation due to AEs (11%) and virologic failure (7%) in the Peg-IFN+RBV group compared with the other treatment groups. The lowest rates of discontinuation due to AEs were observed during 12 and 16 weeks of SOF+RBV treatment (0% to 1%) compared with 4% in the placebo group and 11% in the Peg-IFN+RBV group.

The most commonly reported AEs (≥ 15% of patients in any treatment group) in the individual treatment groups in the FISSION, POSITRON, and FUSION studies and the pooled SOF+RBV 12 Week group from the three studies are presented in Table 41 in Section 7.2.2. The most commonly reported AEs occurred less frequently in patients receiving SOF+RBV than in patients receiving PEG+RBV. The three most commonly reported AEs occurring in the placebo group were similar to those reported for the two

SOF+RBV treatment groups: fatigue, headache, and nausea. The frequency of commonly reported AEs was similar in patients in receiving SOF+RBV treatment for 12 and 16 weeks.

The placebo group had the lowest proportion (1%) and the Peg-IFN+RBV group had the highest proportion (19%) of Grade 3 or 4 AEs compared with the SOF+RBV groups (range, 4% to 8%). No individual Grade 3 or 4 AEs occurred in more than 1% of patients receiving SOF+RBV or placebo. Grade 3 or 4 AEs occurring in more than 1% of patients receiving Peg-IFN+RBV were neutropenia, fatigue, thrombocytopenia, and insomnia. Few serious adverse events (SAEs) were reported in the FISSION, POSITRON, and FUSION studies (≤ 4% patients in any treatment group). The Peg-IFN+RBV group had the lowest proportion of patients with an SAE (1%), and the SOF+RBV groups (4% and 3% for SOF+RBV 12 Week and 16 Week groups) and the placebo group (3%) had similar proportions of patients with an SAE. No individual SAE occurred in more than 1% of patients in any of the treatment groups. One death from cocaine and heroin intoxication occurred on Day 1 of the FISSION study; there were no other treatment-emergent deaths in the Phase 3 registration studies.

The hematology and chemistry laboratory abnormalities in the individual treatment groups in the FISSION, POSITRON, and FUSION studies and the pooled SOF+RBV 12 Week group from the three studies are presented in Table 42 and Table 43 in Sections 7.2.4 and 7.2.5, respectively. Hematological abnormalities were the most commonly reported laboratory abnormalities across all active treatment groups. The number of chemistry abnormalities was low across the active treatment groups (range, 0% to 6%).

Consistent with the expected hemolytic anemia associated with RBV treatment, hemoglobin reductions to < 10 g/dL were observed in all RBV-containing treatment groups: 9% in the pooled SOF+RBV 12 Week group, 5% in the SOF+RBV 16 Week group, 0% in the placebo group, and 14% in the Peg-IFN+RBV group. Despite the higher dose of RBV in the two SOF+RBV groups (1000 or 1200 mg daily) compared with the Peg-IFN+RBV group (800 mg daily), the percentage of patients developing hemoglobin < 10 g/dL during treatment was lower for the SOF+RBV groups than the Peg-IFN+RBV group. A total of 1% of patients in the pooled SOF+RBV 12 Week group developed a hemoglobin level < 8.5 g/dL compared with 2% of patients in the Peg-IFN+RBV group who developed a hemoglobin level < 8.5 g/dL. Based on the RBV prescribing information, the clinical study protocols recommended RBV dose reduction if hemoglobin decreased to < 10 g/dL and RBV dose discontinuation if hemoglobin decreased to < 8.5 g/dL {21450}. Only one patient receiving SOF+RBV discontinued RBV due to anemia. The rate of transfusion in the SOF+RBV groups was < 1%; three patients across both SOF+RBV groups in the Phase 3 registration studies required transfusion.

Consistent with the expected bone marrow suppressive effects of Peg-IFN and the hemolytic effects of RBV, decreased neutrophil counts and hemoglobin were the most commonly reported laboratory abnormalities in the Peg-IFN+RBV control group. No relevant changes in hematology parameters were observed in the placebo group.

SOF administered with RBV was generally safe and well tolerated and the SOF+RBV regimen did not appear to increase the expected incidence or severity of RBV-associated side effects or hematologic effects. Adverse events reported with SOF+RBV treatment include fatigue, headache, nausea, insomnia, and anemia, all of which reflect the AE profile associated with RBV treatment. Increasing the duration of SOF+RBV did not alter the side effect profile of the SOF+RBV treatment. The safety profile of SOF+RBV treatment in patients with compensated cirrhosis was similar to that in patients without cirrhosis.

1.7.2. Safety of SOF+Peg-IFN+RBV Treatment in Patients with Genotype 1, 4, 5, or 6 HCV Infection

In the NEUTRINO study, 98% of patients completed the study treatment (Section 7.1, Table 39). Although 95% of patients had at least one AE, only 2% of patients discontinued the treatment regimen due to an AE. Anemia was the only AE leading to treatment discontinuation in more than 1 patient (2 patients).

The most commonly reported AEs (≥ 15%) in the NEUTRINO study are presented in Table 46 in Section 7.3.2. The three most commonly reported AEs were fatigue, headache, and nausea. The overall AE profile was similar in frequency and the nature of AEs was consistent with the expected profile for Peg-IFN+RBV treatment, which includes hemolytic anemia for RBV and flu-like symptoms (fatigue, pyrexia, myalgia, headache, and rigors), psychiatric reactions (depression, insomnia, irritability, and anxiety), anorexia, nausea and vomiting, neutropenia, diarrhea, arthralgia, injection site reactions, alopecia, and pruritus for Peg-IFN {24700}, {21450}.

Grade 3 AEs occurred in 48 of 327 patients (15%); the most frequently reported Grade 3 AEs were neutropenia (7%) and anemia, fatigue, and headache (2% each). Eight SAEs were reported in 4 patients (1%); no SAE was reported in more than 1 patient. No treatment-emergent deaths were reported.

The hematology and chemistry laboratory abnormalities in the NEUTRINO study are presented in Table 47 and Table 48 in Sections 7.3.4 and 7.3.5, respectively. Hematological abnormalities were the most commonly reported laboratory abnormalities. The number of chemistry abnormalities was low (range, 0% to 3%).

Consistent with the expected bone marrow suppressive effects of Peg-IFN and the hemolytic effects of RBV, reductions in neutrophil count and hemoglobin were the most frequently reported laboratory abnormalities {24700}, {21450}. Based on the RBV prescribing information, the clinical study protocol recommended RBV dose reduction if hemoglobin decreased to < 10 g/dL and RBV dose discontinuation if hemoglobin decreased to < 8.5 g/dL {21450}. The proportion of patients developing hemoglobin < 10 and < 8.5 g/dL during treatment was 23% and 2%, respectively. RBV dose reductions occurred in 20% of patients. Two patients discontinued the treatment regimen due to anemia. Three patients received blood transfusions as treatment for anemia.

Based on the Peg-IFN prescribing information, the clinical study protocol recommended Peg-IFN dose reduction if the neutrophil count decreased to < 750/mm^3 {24700}. Neutropenia or decreased neutrophil count resulted in Peg-IFN dose modifications in 16% of patients. One patient discontinued Peg-IFN due to neutropenia.

The overall AE profile of SOF+Peg-IFN+RBV treatment was similar to that expected of an interferon- and RBV-containing treatment without apparent increases in severity of expected events or unexpected events in patients with genotypes 1, 4, 5, and 6 HCV infection. The safety profile of the SOF+Peg-IFN+RBV regimen in patients with compensated cirrhosis was similar to that in patients without cirrhosis.

1.8. SOF+RBV Treatment in Patients Awaiting Liver Transplantation

This ongoing Phase 2, open-label study (P7977-2025) is evaluating the efficacy of SOF+RBV administered prior to liver transplantation to prevent HCV infection recurrence following liver transplantation in 61 patients with genotypes 1 through 6 HCV infection and hepatocellular carcinoma who are within 1 year of an anticipated liver transplantation (Sections 6.2.8 and 7.4). The primary efficacy endpoint was proportion of patients with pTVR (defined as HCV RNA < LLOQ at Week 12 after transplantation. The median exposure to SOF+RBV treatment was 21 weeks, with a range of 2 to 42 weeks.

In this study to 28 June 2013, 35 of 37 patients have been followed to post-transplantation Week 12 and 23 of these patients (66%) have achieved a pTVR. Of the 24 patients who have reached post-transplantation Week 24, 17 patients (71%) had HCV RNA < LLOQ. No S282T mutations were observed in any patient post-transplantation with recurrent HCV infection. Importantly, the prevention of reinfection of the liver graft appears to be independent of the duration of SOF+RBV treatment received prior to transplantation, provided patients have HCV RNA < LLOQ at the time of transplantation.

Treatment with SOF+RBV was well tolerated for up to 42 weeks in HCV-infected patients with hepatocellular carcinoma awaiting liver transplantation. As compared with the SOF+RBV safety data in the primary safety population, there were higher rates of Grade 3 or 4 AEs, SAEs, and deaths, which can be attributed to the more advanced stage of liver disease and malignancy in these patients. Two patients died prior liver transplantation: one due to acute renal failure in the setting of bacterial peritonitis and sepsis and one due to pneumonitis. Both patients had discontinued treatment with SOF+RBV due to these events. Eleven patients experienced at least one SAE, none of which were considered related to study drug by the investigator. Hepatocellular carcinoma, pyrexia, and obstructive umbilical hernia were the SAEs reported in greater than one patient (2 patients each).

Grade 3 and 4 laboratory abnormalities occurred in 34% and 10% of patients, respectively. Decreases in hemoglobin were attributed to RBV dosing. No abnormality led to a discontinuation of study treatment since no stopping criteria were met for any patient.

SOF, with its safety and minimal drug-drug interaction profile, is uniquely suited for use in patients with chronic HCV infection awaiting liver transplantation to prevent recurrent disease following transplantation.

1.9. Benefit/Risk Profile of Sofosbuvir

SOF is the first oral HCV-specific nucleotide polymerase inhibitor with potent, broad anti-viral activity and a favorable safety profile that has allowed the successful treatment of patients infected with all HCV genotypes, including several patient populations without current treatment options. SOF represents a significant therapeutic advance for patients with chronic HCV infection in two major ways:

- SOF in combination with RBV is the first all oral therapy for patients with chronic genotype 2 or 3 HCV infection, many of whom previously failed treatment or could not be treated.

- SOF in combination with Peg-IFN+RBV provides a shorter, simpler, and more effective interferon-containing regimen for patients with chronic genotype 1, 4, 5, or 6 HCV infections.

The SOF clinical development program has demonstrated that the SOF-based treatment regimens studied have a favorable benefit-risk profile.

1.9.1. Benefits of Sofosbuvir Treatment

The benefits of SOF treatment include the following:

- **Favorable clinical pharmacology profile:** SOF is administered as a single, once-daily 400-mg tablet and has few dosing restrictions. It can be taken with or without food, with most other medications, and requires no dose adjustments in most circumstances commonly encountered in clinical practice.

- **High response rates across multiple patient populations with reduced treatment duration:** SOF-based regimens have demonstrated high SVR rates across many patient populations. Patients with genotypes 1, 2, 4, 5, and 6 HCV infection achieved high SVR rates (≥ 86%) in the Phase 3 registration studies. For patients with genotype 3 HCV infection, SVR rates following SOF+RBV treatment are similar to those observed with the standard-of-care, Peg-IFN+RBV, with the added benefits of shorter duration and elimination of interferon. For patients with genotype 2 or 3 HCV infection, the availability of an oral treatment administered for 12 to 16 weeks with improved tolerability will allow treatment of many patients who are ineligible, intolerant, or unwilling to undergo treatment with an interferon-containing regimen, which has traditionally required 24 weeks of therapy. These regimens will provide important new treatment options for patients with genotype 2 or 3 HCV infection who failed to achieve SVR after previous interferon therapy.

- **Minimal risk of viral resistance:** SOF's unique mechanism of action allows it to be administered in all patients with chronic HCV infection across all HCV genotypes, with minimal risk for the emergence of viral resistance and its potential clinical consequences.

- **Favorable safety and tolerability profile with no unique safety signals attributed to SOF:** The AEs and laboratory safety profiles of SOF in combination with RBV or Peg-IFN+RBV are similar to that expected from the drugs with which it is co-administered. Rates of treatment discontinuation and dose reduction with SOF-containing regimens in the clinical development program were lower than those usually observed with the current standard-of-care, Peg-IFN+RBV.

- **Favorable efficacy and safety profiles in special HCV populations:** Emergent data indicate that the efficacy and safety profile across the broad patient population in the Phase 3 registration studies are maintained in those patients with the greatest need, including patients awaiting liver transplantation.

1.9.2. Risks of Sofosbuvir Treatment

The known risks associated with SOF are those associated with the drugs with which is co-administered, RBV or Peg-IFN+RBV. The risks of SOF treatment include the following:

- **RBV:** RBV is teratogenic and embryocidal and has a warning in its prescribing information stating that pregnancy must be avoided during and for six months after treatment. Hemolytic anemia is the most common AE with RBV. Other AEs such as fatigue and insomnia are also commonly associated with RBV. The RBV prescribing information provides guidance for dose reductions required for the management of anemia and other AEs {24149}, {21450}.

- **Peg-IFN:** Peg-IFN has a number of potentially serious side effects and a warning in its prescribing information stating that it may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders {24700}, {24701}. The prescribing information also provides guidance for dose reductions required for the management of hematologic toxicities.

- **Use of SOF in patient populations with limited or no safety and efficacy data:** For a new and highly effective drug such as SOF, there is the potential that it will be used in patient populations with a medical need but for whom there are limited or no safety and efficacy data. In these populations, there is the risk for the occurrence of new or more severe side effects or lack of efficacy. Gilead has ongoing or is initiating studies in patients co-infected with HIV, patients awaiting liver transplantation, patients who are critically ill, patients with significant renal or liver dysfunction, and pediatric patients. Studies to optimize treatment in patients with genotype 3 HCV infection are also ongoing as well as studies for treatment-experienced patients with genotype 1 HCV infection using SOF in combination with the NS5A inhibitor, ledipasvir.

1.9.3. Conclusions

The availability of SOF in combination with other anti-HCV drugs will provide physicians with a new, safe, and effective treatment option for patients with chronic HCV infection. Benefits of treatment with SOF include high response rates with shorter treatment durations than the previous standard-of-care treatments, little risk of the development of resistance, and an improved or similar safety profile to the currently available therapies. For patients with genotype 2 or 3 HCV infection, including those who failed prior treatment or who are ineligible or intolerant to current therapies, it will be the first time that a treatment option is available.

Overall, the results of the SOF development program support the positive benefit/risk profile for the proposed indication for SOF to be administered in combination with other agents for the treatment of chronic HCV infection in adults (Section 1, Table 1).

2. UNMET MEDICAL NEED

2.1. Hepatitis C Virus

Hepatitis C virus (HCV) is a single-stranded ribonucleic acid (RNA) virus transmitted primarily through blood or blood product exposure {10886}. HCV has significant genetic (RNA sequence) variability and is classified on this basis into at least 6 genotypes. The most common genotype in United States (US) is genotype 1, representing 72% to 75% of all cases of chronic HCV infection {25896}, {25892}, {25891}. Genotypes 2 and 3 HCV infections represent the majority of the remaining cases of chronic HCV infection, with approximately 14% to 17% and 8% to 11% of cases, respectively {25896}, {25892}, {25891}. Genotype 4, 5, and 6 HCV infections are most prevalent in the Middle East, South Africa, and Southeast Asia, respectively {22111}. While spontaneous eradication of the infection occurs in 10% to 50% of cases, most patients infected with HCV develop chronic HCV infection {17257}. Chronic HCV infection is a serious, progressive, and potentially life-threatening disease and a major global public health concern. Asymptomatic liver disease progression can occur over several decades {17257},{25133}. If left untreated, 10% to 40% of these patients are expected to develop cirrhosis and would then be at risk for the development and progression of further complications, including bleeding varices, ascites, hepatic encephalopathy, and hepatocellular carcinoma {13693}, {17257}, {17638}.

An estimated 170 million people are chronically infected with HCV worldwide {24854}. In the US, an estimated 3.2 million people have chronic HCV infection, which will lead to approximately 36,000 deaths each year by 2030 {23407}, {25133}, {10937}, {25895}.

Viral eradication of chronic HCV infection, defined as sustained virologic response (SVR), has been associated with histologic improvement of fibrosis, reduced progression of fibrosis, decreased risk of hepatocellular carcinoma, reduced risk of liver decompensation, and overall reduced all-cause and liver-related mortality {6643}, {22614}, {22612}, {22616}. However, estimates also indicate that approximately 50% of patients with chronic HCV infection have been diagnosed and approximately 30% of the diagnosed HCV-infected patients are ineligible for current interferon-based therapies {20451}, {17892}, {3291}, {25895}, {25898}. As a result, less than 15% of diagnosed HCV-infected patients have received treatment {25895}. The reasons that patients are not being treated are many, including that the current standard-of-care treatments, which all include interferon, have significant side effects, the long duration of treatment (24 to 48 weeks), and the suboptimal response rates {24700}, {24701}, {21450}, {24149}, {25285}, {24932}. As a result, there is a large pool of HCV-infected patients— undiagnosed, diagnosed yet untreated, and patients who have failed current therapies—at risk for progression of their liver disease and the attendant morbidity and mortality {21162}.

There are significant sequelae from the chronic liver inflammation associated with chronic HCV infection {17257}. Since the epidemic began more than three decades ago, a growing proportion of patients have developed cirrhosis and its associated complications, including liver decompensation and liver cancer {17257}. In the US, rates of cirrhosis in patients with

chronic HCV infection are projected to be as high as one million patients by 2020 {21162}. Accompanying this increase in cirrhosis, it is also projected that approximately 150,000 and 14,000 patients will develop liver decompensation and liver cancer, respectively {21162}. Because of this burden of advancing disease, chronic HCV infection is now the leading indication for liver transplantation, with approximately 5500 patients awaiting liver transplantation, and this number will continue to increase over future decades {26213}. The aging HCV-infected population, increasing rates of complications, and sequelae of advanced liver disease pose a substantial challenge to health care in the coming decades {23868}.

Chronic HCV infection is unique compared with other chronic viral diseases, such as chronic hepatitis B, human immunodeficiency virus (HIV), and herpes, in that it can be cured. Cure is defined as SVR, defined as loss of the HCV RNA 12 weeks following the end of treatment. SVR has been demonstrated to be a reliable surrogate {22617}, {22618}, {22619}, {22549}, {14641}. For individual patients, normalization of liver enzymes and improvement in liver histology, including reversal of cirrhosis in some patients, has been observed {6643}, {25894}. Importantly, in studies of HCV-infected patients with SVR, the rates of disease progression, liver decompensation, liver cancer, and liver transplantation are reduced as well as the rates of all-cause and liver-related mortality{24244}, {23851}, {25891}, {25890}.

2.2. Current Treatment Options for HCV Treatment

Table 8 summarizes the currently recommended treatment regimens for patients with chronic HCV infection with genotypes 1 through 6 based on the American Association for the Study of Liver Diseases (AASLD) treatment guidelines. Historically, a once-weekly subcutaneous injection of pegylated interferon (Peg-IFN) and twice-daily oral ribavirin (RBV) for 24 or 48 weeks was the standard-of-care treatment for chronic HCV infection, with varying SVR rates observed among the HCV genotypes {13693}, {19759}. Recently, a new standard-of-care treatment of 12 to 44 weeks of an oral protease inhibitor in combination with 24 to 48 weeks of Peg-IFN+RBV, with duration of therapy guided by the on-treatment response, was approved for patients with chronic genotype 1 HCV infection {19759}, {25285}, {24932}. No new agents have been approved in recent years for the treatment of patients infected with HCV genotypes 2 through 6.

Table 8. Recommended Treatment Regimens for Genotypes 1 Through 6 HCV Infection According to AASLD Treatment Guidelines

Genotype	Current Recommended Treatment for Patients Who are Interferon Eligible			
	Treatment-Naive Patients	**Approximate SVR Rates**	**Treatment-Experienced Patients**	**Approximate SVR Rates**
1	PI+Peg-IFN+RBV[a]	63% to 79%	PI+Peg-IFN+RBV[a]	32% to 86%
2	Peg-IFN+RBV for 24 weeks	75% to 90%		N/A
3	Peg-IFN+RBV for 24 weeks	66% to 80%		N/A
4	Peg-IFN+RBV for 48 weeks	50% to 80%	No recommended treatment	N/A
5	No recommended treatment	N/A		N/A
6	Peg-IFN+RBV for 48 weeks	60% to 80%		N/A

AASLD = American Association for the Study of Liver Diseases; N/A = not applicable; Peg-IFN = pegylated interferon; PI = protease inhibitor (boceprevir and telaprevir); RBV = ribavirin; SVR = sustained virologic response

Note: Recommendations are approved by AASLD, the Infectious Diseases Society of America, and the American College of Gastroenterology.

a For the protease inhibitors, boceprevir and telaprevir, the overall duration of therapy is response guided for a total of 24 to 48 weeks.

b Following treatment with telaprevir in combination with Peg-IFN and RBV, the SVR rates for prior relapsers, prior partial responders, and prior null responders were 86%, 59%, and 32%, respectively. Following treatment with boceprevir in combination with Peg-IFN and RBV, the SVR rates for prior relapsers and prior partial responders were 70% to 75% and 40% to 52%, respectively.

Source: {22635},{22442}, {24700}, {21450}, {22604}, {22605}, {21319}, {22602}, {24932}, {25285}, {13693}, {19711}

2.2.1. Limitations with Current HCV Therapies

The current treatment options for chronic HCV infection vary by viral genotype and are associated with toxicities that pose significant challenges for patient management {24700}, {24701}, {21450}, {24149}, {24932}, {25285}. High rates of treatment discontinuation due to adverse events (AEs) or reduced efficacy due to toxicity-driven dose reductions are common {24700}, {24701}, {21450}, {24149}. Furthermore, the tolerability of Peg-IFN+RBV-containing regimens is reduced in certain patient populations that also have the greatest clinical need, including the elderly and patients with cirrhosis. The toxicity and tolerability issues associated with interferon-containing regimens, including those regimens that contain HCV-specific protease inhibitors, has led to the inability or unwillingness of many patients to be treated. Additionally, a substantial number of patients are not eligible to receive Peg-IFN and/or RBV due to absolute or relative contraindications including the following {22624}, {20450}, {17893}, {24700}, {17892}, {3291}, {17257}:

- Patients with currently uncontrolled or history of significant depression, psychosis, epilepsy, autoimmune disease, bipolar disorders, schizophrenia, or anxiety disorders

- Patients with severe or poorly-controlled concurrent medical disease(s), such as hypertension, coronary artery disease, heart failure, diabetes, chronic obstructive pulmonary disease, and thyroid diseases

- Patients with abnormal hematological indices

- Patients with decompensated liver disease

- Female patients of child-bearing age or male patients with female partner of child-bearing potential who do not want to delay conception

In addition to the above absolute or relative contraindications, the fear of side effects and complexity of treatment have also been recognized as major barriers to treatment {23858}.

The impact of these limitations on the number of patients eligible for treatment has been evaluated in a number of small studies. In a study of veterans with chronic HCV infection, 68% of patients (n = 100) were ineligible for interferon-containing treatment, and of those, 32% had more than one ineligibility criterion. The most common reasons for ineligibility for interferon-containing treatment were hazardous alcohol consumption and severe mental illness {17892}. In a study of patients with HCV infection in a metropolitan clinic in the US, 72% of patients (n = 293) were not treated. The reasons for not treating these patients included the following: nonadherence to evaluation and education (37%), medical contraindications to interferon-containing treatment (34%), substance abuse (13%), patient preference (11%), and normal alanine aminotransferase (ALT) levels (5%) {3291}.

Although patients with chronic genotype 1 HCV infection treated with a protease inhibitor in combination with Peg-IFN+RBV have significantly improved efficacy outcomes compared with treatment with Peg-IFN+RBV only, both telaprevir and boceprevir have attributes that limit their effectiveness. Their genotype-specific anti-viral activity limits their use to patients with genotype 1 HCV infection {24932}, {25285}. In addition, patients with bridging fibrosis or cirrhosis have lower SVR rates after treatment with Peg-IFN+RBV or a protease inhibitor in combination with Peg-IFN+RBV {22453}, {22442}, {24932}, {25285}. The approved protease inhibitors are also associated with higher rates of side effects including skin disorders (telaprevir) and anemia (boceprevir and telaprevir) {24932}, {25285}. In patients receiving telaprevir in combination with Peg-IFN+RBV, fatal and nonfatal serious skin reactions including Stevens-Johnson syndrome, drug reactions with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis have all been reported {24932}. For these reasons, the telaprevir labeling was recently updated with a boxed safety warning regarding the serious and potentially fatal skin reactions and states that treatment must be immediately stopped in patients experiencing a rash with systemic symptoms or any progressive severe rash.

Both telaprevir and boceprevir are also inhibitors of cytochrome P450 (CYP) enzyme 3A4 and therefore have the potential to have clinically significant drug-drug interactions with medications that are frequently used in patients with HCV infection, including patients coinfected with HIV {24932}, {25285}. Both regimens require three times daily dosing, a

high pill burden, and complex response-guided treatment algorithms with differing durations of treatment. In addition, patients with genotype 1 HCV infection who fail current therapy with a protease inhibitor in combination with Peg-IFN+RBV therapy usually develop non-structural protein 3 (NS3) protease inhibitor resistance. The long-term consequences of these resistance mutations for potential future treatment outcomes are currently unknown.

2.2.2. Conclusions

With the limitations of the currently available treatments, there is a clear unmet medical need for safer, simplified HCV-treatment regimens that are effective across all HCV genotypes. Therapies with improved tolerability that are either interferon-free (thereby eliminating the treatment-associated toxicities of Peg-IFN) or that can shorten the duration when combined with Peg-IFN+RBV are likely to provide significant benefit. In particular, the development of a treatment regimen for chronic HCV infection that eliminates or reduces the need for Peg-IFN has the potential to substantially impact the global incidence, prevalence, and burden of HCV infection for patients, health care providers, and the medical system as a whole. New treatment options are especially crucial in patient populations where treatment with Peg-IFN is not possible, including those who have failed prior therapy.

2.3. Rationale for Development of Sofosbuvir

Gilead has developed the direct-acting anti-viral (DAA) agent sofosbuvir (SOF) for the treatment of chronic HCV infection. The regimen of SOF+RBV was developed to provide the first highly effective all-oral regimen for the treatment of patients with genotype 2 or 3 HCV infection with a shorter duration of administration (12 weeks for genotype 2 and 16 weeks for genotype 3) and enhanced safety and tolerability compared with currently available Peg-IFN+RBV-based regimens. Treatment with SOF+RBV provides a promising regimen for patients with genotype 2 or 3 HCV infection that do not require administration of Peg-IFN. These regimens offer a major advance in treatment, and for some genotype 2 or 3 HCV-infected patient populations, will provide treatment where no adequate therapy currently exists (ie, patients with genotype 2 or 3 HCV infection who are interferon ineligible, interferon intolerant, or unwilling to take interferon and those who have failed prior therapy with Peg-IFN+RBV).

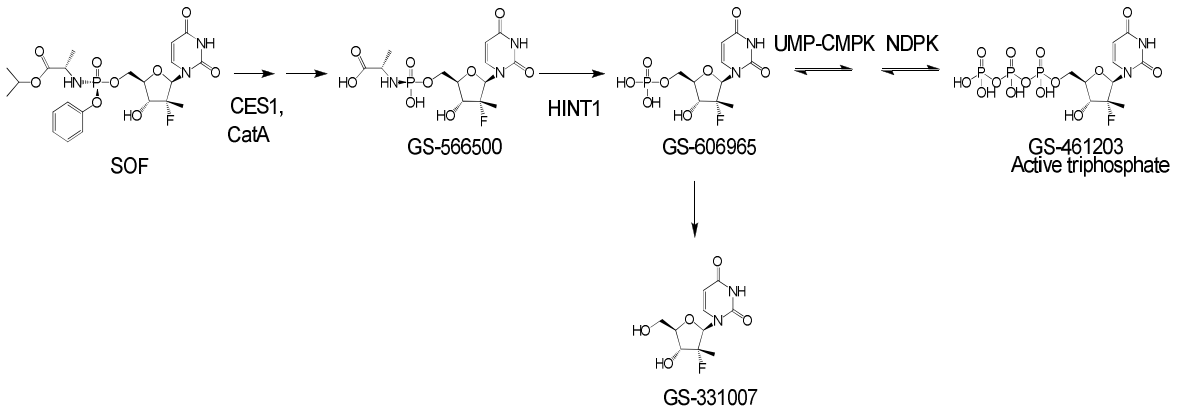
Although elimination of both Peg-IFN and RBV from a treatment regimen is the ultimate goal for the treatment of chronic HCV infection, increasing the efficacy of a Peg-IFN-containing regimen while shortening treatment duration could substantially improve treatment for a large number of patients with genotype 1, 4, 5, or 6 HCV infection. Flu-like symptoms typically peak and may largely resolve within the first month of Peg-IFN-based therapy, whereas neuropsychiatric symptoms and fatigue become more prevalent and severe with cumulative exposure {20487}. Therefore, shortening the treatment duration to 12 weeks with the highly effective regimen of SOF+Peg-IFN+RBV would enable more patients to successfully complete a treatment course. In addition, the high probability of therapeutic success would likely motivate patients to remain compliant and complete their treatment course despite Peg-IFN-related AEs earlier in treatment. Lastly, a shorter treatment duration combined with a highly effective, simplified course of therapy would likely result in greater numbers of patients with chronic HCV infection who may benefit from and subsequently receive treatment in the near term.

3. NONCLINICAL DEVELOPMENT PROGRAM

A comprehensive program of nonclinical studies with SOF has been conducted, including primary and secondary pharmacodynamics; safety pharmacology; absorption, distribution, metabolism, and elimination; and toxicology studies which support the favorable benefit/risk profile of SOF.

Figure 1 presents the intracellular activation pathway of SOF, which has been completely characterized {18608}. The first step in the intracellular activation is cleavage of the isopropyl ester catalyzed by carboxylesterase 1 (CES1) or cathepsin A (CatA). Subsequent activation steps include removal of the amino acid from GS-566500 by histidine triad nucleotide-binding protein 1 (HINT1) to release the nucleoside analog monophosphate GS-606965 and sequential phosphorylation by uridine monophosphate-cytidine monophosphate (UMP-CMP) and nucleoside diphosphate kinases (NDPKs) to form the nucleoside analog diphosphate and, ultimately, the pharmacologically active triphosphate metabolite GS-461203. The intracellular activation of SOF is mediated by low-affinity and high capacity hydrolase (CES1, CatA, and HINT1) and nucleotide phosphorylation (UMP-CMP kinase and NDPK) pathways that are not readily inhibited at pharmacologically relevant concentrations achieved by agents that may be co-administered to patients with HCV infection.

Figure 1. Intracellular Metabolic Pathway of Sofosbuvir



CatA = cathepsin A; CES1 = carboxylesterase 1; GS-331007 = 2'-deoxy-2'-fluoro-2'-C-methyluridine; GS-461203 = 2'-deoxy-2'-fluoro-2'-C-methyluridine-triphosphate; GS-566500 = 2'-deoxy-2'-fluoro-2'-C-methyluridine-monophosphate-L-alanine; GS-606965 = 2'-deoxy-2'-fluoro-2'-C-methyluridine-monophosphate; HINT1 = histidine triad nucleotide-binding protein 1; NDPK = nucleoside diphosphate kinase; SOF = sofosbuvir; UMP-CMPK = uridine-monophosphate/cytidine-monophosphate kinase

GS-9851, the diastereomeric mixture containing SOF, was used in early nonclinical and clinical studies, but an enriched mixture with ≥ 98% of the single diastereomer SOF was chosen for development and registration. Pivotal toxicology studies were conducted with SOF. GS-9851 contains 2 diastereomers, SOF and GS-491241, in an approximate 1:1 ratio.

There is no evidence of interconversion in vitro or in vivo. As both diastereomers produce the same metabolites including the pharmacologically active triphosphate, data generated with either diastereomer inform the safety of SOF.

3.1. Nonclinical Pharmacology

3.1.1. Mechanism of Action

SOF is a novel HCV non-structural protein 5B (NS5B)-directed inhibitor that displayed potent inhibition of HCV RNA replication in vitro. In human hepatocytes, SOF is converted to the pharmacologically active uridine triphosphate form, GS-461203. GS-461203 is a potent inhibitor of the NS5B polymerase with concentrations that resulted in 50% inhibition (IC_{50} values) ranging from 0.7 to 2.6 µM. GS-461203 binds to the active site of HCV polymerase and incorporates into the elongating HCV RNA chain as a chain terminator. The active site of HCV NS5B polymerase is well conserved across all genotypes, consistent with the observed broad genotypic activity of SOF.

3.1.2. In Vitro Activity

In vitro, SOF demonstrated potent pan-genotypic activity across the HCV genotypes (1a, 1b, 2a, 2b, 3a, 4a, 5a, and 6a) at concentrations of SOF-inhibiting virus replication by 50% (EC_{50} values) of 0.014 to 0.11 µM. When tested against a panel of genotype 1a, 1b, 2b, and 3a clinical HCV isolates, SOF demonstrated similar EC_{50} values to the above laboratory strains of corresponding genotypes. In vitro combination studies showed an additive interaction between SOF and interferon. A minor synergy was observed for the combination of SOF with RBV. No antagonism was observed for any of the combinations tested.

3.1.3. In Vitro Resistance and Cross-resistance Characterization

In vitro resistance selections in replicon cells were performed to determine which NS5B mutations might likely confer resistance to SOF. S282T was the primary mutation selected in all replicon genotypes tested and site-directed mutagenesis confirmed that S282T conferred reduced susceptibility to SOF; however, the S282T mutation did not confer cross-resistance to other classes of anti-viral inhibitors and appeared to increase sensitivity to RBV in vitro. HCV replicons expressing the S282T mutation also showed reduced replication capacity in vitro. Conversely, SOF remained fully active against replicons harboring mutations that conferred resistance to protease inhibitors, nonnucleoside inhibitors, non-structural protein 5A (NS5A) inhibitors, nucleoside inhibitors (NS5B L159F and L320F), as well as the RBV-associated mutants F415Y and T390I. These data support the potential utility of other DAAs in combination with SOF for treatment of chronic HCV infection.

3.1.4. Selectivity

Table 9 shows SOF cytotoxicity in human cell lines and primary cells. SOF showed little or no cytotoxicity in 5-day assays with cell lines derived from liver, prostate, lymphoid, or connective tissues or primary human cells isolated from the liver, circulating lymphoid cells, or bone marrow.

Table 9. Sofosbuvir Cytotoxicity in Human Cell Lines and Primary Cells

Cell Line CC_{50} (µM)[a]				
Liver		**Prostate**	**Fibroblast**	**T-Cell**
Huh7	**HepG2**	**PC-3**	**MRC5**	**MT-4**
66	> 89	> 89	> 89	> 100
Primary Cell CC_{50} (µM)				
Liver	**Peripheral Blood Mononuclear Cells**		**Bone Marrow**	
Hepatocyte	**Quiescent**	**Stimulated**	**Erythroid**	**Myeloid**
> 100	> 100	> 100	> 50[b]	> 50[b]

CC_{50} = concentration that results in 50% cytotoxicity

a Cytotoxicity determined in 5-day assays in cell lines and primary cells except for erythroid and myeloid bone marrow cells that were treatment for 14 days.

b Tested using SOF-containing diastereomeric mixture GS-9851 {21144}.

Table 10 shows the activity of the pharmacologically active triphosphate, GS-461203, on human polymerases. GS-461203 was not an inhibitor of human deoxyribonucleic acid (DNA) polymerase (POL) involved in DNA replication (POL α) or repair (POL β), or the transcriptional RNA POL (POL II) in biochemical assays (IC_{50} > 200 µM). GS-461203 also did not inhibit the mitochondrial DNA POL (POL γ; IC_{50} > 200 µM) or RNA POL (mitochondrial RNA polymerase [mtRNAP]; IC_{50} > 500 µM). Consistent with the lack of inhibition of the mitochondrial DNA POL γ, SOF did not deplete mitochondrial DNA following treatment of the liver cell line Hep G2 for 10 days at the highest concentration tested (20 µM). Consistent with the lack of inhibition of mtRNAP and RNA POL II, SOF did not markedly reduce expression of the mitochondrial transcript cytochrome c oxidase subunit 1 (COX1) or nuclear transcript succinate dehydrogenase complex, subunit A (SDHA) following 5 days treatment of the prostate cell line PC-3 at the highest concentration tested (100 µM). In contrast, 2',3'-dideoxycytidine (ddC), whose active triphosphate is a potent inhibitor of mitochondrial DNA POL γ, inhibited DNA production and selectively depleted COX1 protein expression at sub-micromolar concentrations when tested side-by-side in these assays.

Table 10. Inhibition of Human Polymerases by the Pharmacologically Active Triphosphate Metabolite of Sofosbuvir, GS-461203

	IC_{50} (μM)[a]				
	DNA Pol α	**DNA Pol β**	**DNA Pol γ**	**RNA Pol II**	**mtRNAP**
GS-461203	> 200	> 200	> 200	> 200	> 500
Controls (IC_{50})	Aphidicolin (7.3)	3'-dTTP (1.4)	3'-dTTP (0.74)	α-amanitin (0.0024)	3'-dGTP (1.9)

DNA = deoxyribonucleic acid; GS-461203 = 2'-deoxy-2'-fluoro-2'-C-methyluridine triphosphate; 3'dGTP = 3'-doexy-guanosine triphosphate; 3'dTTP = 3'-deoxy-thymidine triphosphate; IC_{50} = concentration that results in 50% inhibition; mtRNAP = mitochondrial RNA polymerase; POL = polymerase

a IC_{50} determined for natural nucleotide incorporation into model primer/templates by each polymerase.

3.2. Safety Pharmacology

SOF, when administered as a component of GS-9851, has no pharmacologically significant off-target binding affinity to the 171 receptors, enzymes, and ion channels tested. SOF had no clinically relevant effect on vital organ systems in the central nervous system, respiratory, and cardiovascular safety pharmacology studies.

3.3. Pharmacokinetics and In Vitro Drug Interactions

SOF effectively delivers the nucleoside analog monophosphate to the liver for subsequent conversion to the pharmacologically active triphosphate after oral administration.

Following oral administration of SOF to dogs, high levels of the pharmacologically active triphosphate GS-461203 were efficiently formed in the liver and persisted with an estimate half-life of 17.8 hours. SOF undergoes extensive hepatic extraction and hydrolase cleavage leading to high relative exposures to the nucleoside metabolite GS-331007 which accounted for > 80% of the total plasma exposure to drug-related material across species. Tissue distribution studies in the rat found high concentrations in the liver and lymphatic system (maximal concentrations ≥ 10-μg SOF equivalents/g). Liver to plasma concentration ratios were greater than or equal to 15:1. SOF poorly penetrated the blood-brain barrier with low levels observed in the central nervous system (maximal concentrations < 1-μg SOF equivalents/g).

SOF and its predominant metabolite GS-331007 do not meaningfully interact with traditional hepatic drug metabolism pathways. When tested with recombinant enzymes, SOF and GS-331007 were not inhibitors of CYP isoforms 1A2, 2C8, 2C9, 2C19, 2D6, and 3A4 (IC_{50} > 100 μM) and neither was a substrate for these isoforms or 1A or 2B6. SOF and GS-331007 metabolism in hepatic subcellular fractions were not affected by addition of the cofactor for uridine diphosphate glucuronosyltransferase (UGT) 1A1 and they showed little or no inhibition of this enzyme (IC_{50} > 50 μM). In primary human hepatocytes, SOF caused little or no induction in CYP activities or increases in CYP messenger RNA (mRNA); the small increases in CYP2B6 activity and CYP2B6 and CYP3A4 mRNA levels observed only

at SOF 100 μM were < 15% of those caused by the positive controls, phenobarbital and rifampin, respectively.

SOF was found not to meaningfully interact with hepatic transporters organic anion transporting polypeptides (OATP) 1B1 and 1B3 or organic cation transporter (OCT) 1 that are expressed on the basolateral membrane of the liver and can facilitate the uptake of substrates into the liver. Furthermore, the lack of meaningful OATP1B1, OATP1B3, UGT1A1, or multi-drug resistance related protein 2 (MRP2) inhibition suggests that SOF is unlikely to interfere with bilirubin elimination. SOF did not inhibit the bile salt efflux pump (BSEP; IC_{50} > 100 μM). While SOF has a low potential to be involved in systemic drug-drug interactions, it is a substrate but not an inhibitor of P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP). Therefore, the intestinal absorption of SOF may be decreased by co-administration with inducers of the expression of these transporters or increased by co-administration with inhibitors of these transporters. Potent efflux transport inhibitors including cyclosporin A were observed to increase absorptive permeability by reducing the efflux transport of SOF in the in vitro Caco-2 intestinal absorption model.

SOF drug-related material is almost exclusively eliminated from the body renally as the nucleoside metabolite GS-331007. Renal elimination of GS-331007 is mediated by a combination of glomerular filtration and active tubular secretion. GS-331007 is not an inhibitor or substrate of transporters that are expressed in the proximal tubule that are known to mediate the active tubular secretion of xenobiotics and that have been implicated in renal drug-drug interactions (BCRP, multidrug and toxin extrusion 1 [MATE1], MRP2, organic anion transporter [OAT] 1, OAT3, OCT2, and Pgp).

3.4. Nonclinical Toxicology

The toxicology profile of SOF is well characterized in multiple animal species. The complete nonclinical program included single-dose oral toxicity study in rats; repeat-dose oral toxicity studies in mice (up to 13 weeks), rats (up to 26 weeks), and dogs (up to 39 weeks); genotoxicity tests in vitro and in vivo; a full development and reproductive toxicity program; and 2-year oral carcinogenicity studies in mice and rats which are ongoing.

The nonclinical toxicity studies demonstrate that SOF is generally well tolerated for up to 6 months in the rat and 9 months in the dog, with no observed adverse effect levels (NOAELs) providing margins of exposure relative to the exposures in patients treated with the recommended clinical dose (400 mg) of 9-fold (rat) and 13-fold (dog) for GS-331007.

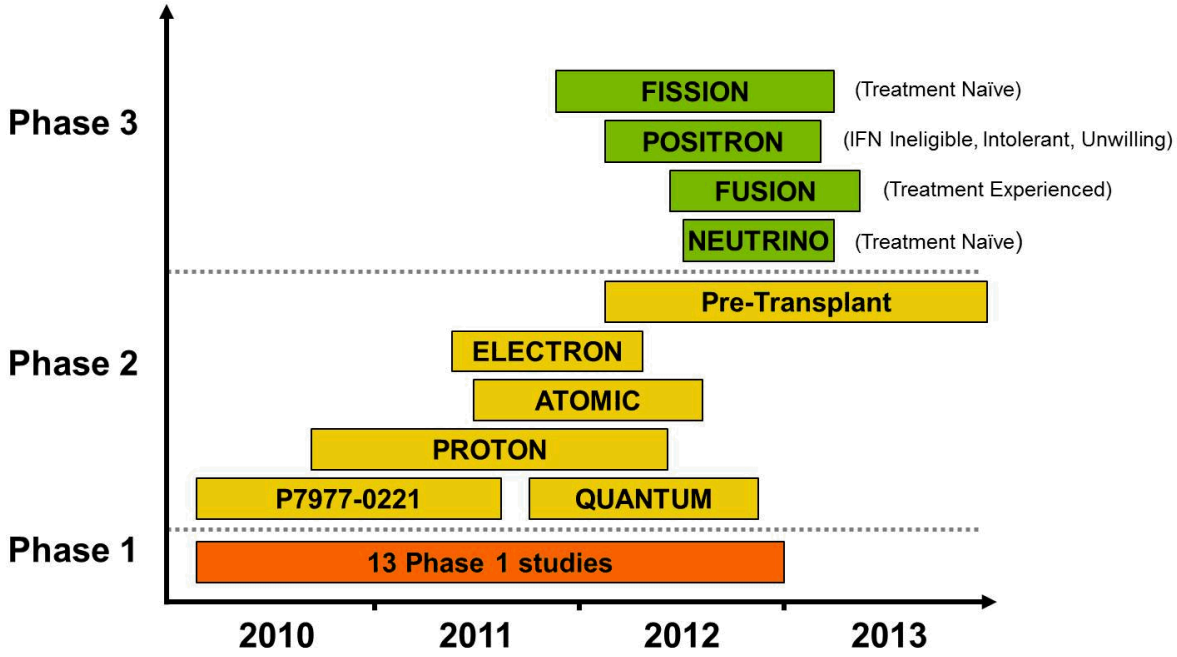
Target organ toxicities were identified in short-term dose range finding studies (7 days) at very high doses and included the cardiovascular (rats; 2000 mg/kg/day, lethal dose) and hepatobiliary (dogs; 1500 mg/kg/day, poorly tolerated dose) systems. At these high doses, margins of exposure of GS-331007 relative to the clinical exposure at SOF 400 mg were 29-fold and 123-fold in the rat and dog, respectively. Effects on the gastrointestinal (rats and dogs) and hematopoietic (dogs) systems were minimal and were not considered adverse.

SOF is considered non-genotoxic and had no effects on fertility, embryo-fetal and pre- and post-natal development at exposures at least 10-fold greater than the mean clinical exposure at SOF 400 mg. SOF was negative for delayed-type hypersensitivity and was not considered a skin or eye irritant.

4. CLINICAL DEVELOPMENT PROGRAM

Figure 2 shows the key clinical studies in the SOF clinical development program to support this New Drug Application (NDA) submission. A total of 23 key Gilead-sponsored studies have been conducted, including four Phase 3 registration studies, five Phase 2 studies, 13 Phase 1 studies, and one pre-transplant study.

Figure 2. Key Studies in Sofosbuvir Clinical Program



IFN = interferon

Preliminary data from three collaborative studies were included in the NDA submission: the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored SPARE study with SOF and RBV, Bristol-Myers Squibb (BMS)-sponsored Study A1444040 with SOF and daclatasvir (DCV) with and without RBV, and Janssen Pharmaceuticals, Inc. (Janssen) Study HPC2002 with SOF and simeprevir (SMV) with and without RBV.

Overall, 2935 HCV-infected patients received at least one dose of SOF 400 mg in Phase 2 or 3 studies. Of these patients, 2356 received treatment for at least 12 weeks, 818 received treatment for at least 16 weeks, and 709 received treatment for 24 weeks. In addition to the studies provided in the NDA submission, Appendix 1 provides a list of key ongoing studies.

5. CLINICAL PHARMACOLOGY

Table 11 provides an overview of the 13 Phase 1 clinical pharmacology studies completed in the SOF clinical program.

Table 11. Overview of Phase 1 Clinical Pharmacology Studies

Type of Study	Study Number	n	Study Objective
Comparative BA/BE Studies in Healthy Patients	GS-US-334-0131 (Cohort 5)[a]	16	Comparative BA/BE study evaluating PK equivalence between SOF Forms I and II in healthy subjects
	P7977-0111	24	Comparative BA/BE study evaluating GS-9851 200 mg and SOF 200 mg and food effect for SOF in healthy subjects
	P7977-1318	40	Comparative BA/BE study evaluating food effect for 2 formulations of SOF in healthy subjects
PK and Initial Tolerability Studies in Healthy Patients	P7977-0312	7	Mass balance study evaluating SOF in healthy subjects
	P7851-1101	42	First-in-human single-dose PK study evaluating GS-9851 25, 50, 100, 200, 400, and 800 mg in healthy subjects
PK and Initial Tolerability Study in HCV-Infected Patients	P7851-1102	40	Multiple-dose PK study evaluating GS-9851 50, 100, 200, and 400 mg in patients with genotype 1 HCV infection
Intrinsic Factor PK Studies	P7977-0915	30	Single-dose PK study evaluating SOF in patients with various degrees of renal impairment and matched healthy control subjects
	P2938-0515	17	Multiple-dose PK/PD study evaluating SOF in patients with HCV infection with various degrees of hepatic impairment
Extrinsic Factor PK Studies	GS-US-334-0131 (Cohorts 1-4) [a]	72	Drug-drug interaction study evaluating SOF and ARV combinations (EFV/FTC/TDF, DRV/r, RAL, and RPV) in healthy subjects
	P7977-0814	15	Drug-drug interaction study evaluating SOF and methadone in healthy subjects on stable methadone therapy
	P7977-1819	40	Drug-drug interaction study evaluating SOF and cyclosporin A or tacrolimus in healthy subjects
	P7977-1910 (Part A)	34	Drug-drug interaction study evaluating SOF and ARV combinations (ATV/r, EFV, TDF, FTC, ZDV, 3TC, DRV/r, or RAL) in HCV/HIV-coinfected patients
PK/PD and PD Studies in Healthy Patients	P7977-0613	60	Single-dose study evaluating the effect of SOF at therapeutic and supratherapeutic doses (1200 mg) on QT/QTc interval in healthy subjects
PK/PD and PD Studies in HCV-Infected Patients	P2938-0212	30	Multiple-dose PK/PD study evaluating SOF in patients with genotype 1 HCV infection

3TC = lamivudine; ARV = anti-retroviral; ATV = atazanavir; BA = bioavailability; BE = bioequivalence; DRV = darunavir; EFV = efavirenz; FTC = emtricitabine; HCV = hepatitis C virus; PD = pharmacodynamic; PK = pharmacokinetic; /r = boosted with ritonavir; RAL = raltegravir; RPV = rilpivirine; SOF = sofosbuvir; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Note: Unless otherwise indicated, the dose of SOF was 400 mg.

a The first four cohorts of Study GS-US-334-0131 evaluated drug-drug interactions and the fifth cohort evaluated PK equivalence between SOF Form I and II.

Additionally, population pharmacokinetic (PK) analysis for SOF and GS-331007 was performed on all patients with evaluable PK enrolled in the Phase 3 program (n = 986; the only difference in this dataset from the full analysis set was the exclusion of 5 patients without GS-331007 AUC_{tau} estimates).

In addition to the clinical pharmacology studies provided in the NDA submission, an ongoing drug-drug interaction study is evaluating the effect of oral contraceptive on the PK of SOF; Appendix 1 provides a list of key ongoing studies.

5.1. Clinical Pharmacokinetics

Non-clinical characterization of the disposition of SOF across species revealed that SOF was extensively metabolized that led to low systemic exposure of SOF and predominantly systemic exposure to two major metabolites in humans: GS-566500 and the primary circulating metabolite GS-331007 (Section 3).

A mass balance study confirmed these findings and showed that SOF, GS-566500, and GS-331007 accounted for approximately 4%, approximately 7%, and > 90% of drug-related material (ie, total ^{14}C radioactivity), systemic exposure by AUC, respectively. No new metabolites were identified in humans. Due to the low exposure and rapid disappearance of SOF and plasma predominance with linear PK observed for GS-331007, GS-331007 was considered to be the primary analyte of interest in clinical pharmacology assessments.

5.2. Pharmacokinetic Profiles

5.2.1. Absorption

Following oral administration of SOF, peak SOF concentrations were generally observed approximately 0.5 to 2 hours post-dose, regardless of the dose level administered, in patients with HCV infection and healthy subjects. Peak plasma concentrations of GS-331007 were generally observed between 2 to 4 hours after SOF administration. Results from the food effect study demonstrated that a high-fat meal resulted in a slower rate of absorption of SOF with no substantial alteration in the extent of absorption compared with fasted conditions. When evaluated as GS-331007, modestly decreased C_{max} values (24% to 30% lower) were observed while AUC values ($AUC_{0\text{-}last}$ and AUC_{inf}) were unchanged. Dosing of SOF in Phase 2 and 3 clinical studies was recommended without regard to food. However, in all of the Phase 3 studies included in this application, SOF was coadministered with RBV, which is dosed with food per RBV prescribing information {21450}.

5.2.2. Distribution

In vitro protein binding (ultrafiltration studies) of SOF was low in dog and human plasma (< 70%) and constant regardless of protein concentration in human plasma; ex vivo plasma protein binding of SOF were approximately 82% and 85% in healthy subjects and subjects with end-stage renal disease (ESRD), respectively. After a single 400-mg dose of [^{14}C]-SOF in healthy male subjects, the blood to plasma ratio of ^{14}C-radioactivity was approximately

0.71, indicating that SOF and its metabolites were predominantly distributed to plasma relative to the cellular components of blood.

5.2.3. Metabolism and Elimination

In vitro assays demonstrated that SOF, GS-566500, and GS-331007 were minimally metabolized by CYP, flavin monooxygenase (FMO), and UGT enzymes; therefore, SOF and its major metabolites should not be affected (victim drug) by co-administration with inhibitors of CYP isozymes, FMO enzymes, or UGT enzymes (Section 3.3).

Following administration of a single-oral dose of [^{14}C]-SOF to healthy male subjects, SOF was rapidly absorbed. Mean total recovery of the radioactive dose was > 92%, consisting of approximately 80%, 14%, and 3% recovered in urine, feces, and expired air, respectively. These results indicated that ≥ 80% of the administered dose was absorbed into systemic circulation and that renal excretion was the primary route of elimination. The majority (> 90%) of drug related material in the systemic circulation was GS-331007, and correspondingly 78% of the dose was recovered in the urine as GS-331007. Recovery of SOF, as unchanged drug, in the urine and feces was low. Consistent with substantial excretion of GS-331007 in the urine, clinically significant changes in GS-331007 PK were noted with marked (severe, glomerular filtration rate [GFR] < 30 mL/min) renal impairment (Section 5.2.8).

5.2.4. Sofosbuvir Pharmacokinetics after Single- and Multiple-Dose Administration in Healthy Subjects

SOF, a nucleotide analog prodrug, undergoes intrahepatic sequential metabolism to form the long-lived active nucleoside triphosphate analog, GS-461203, that makes SOF suitable for once-daily administration.

SOF and GS-331007 exhibited similar PK upon single- and multiple-dose administration with minimal accumulation of SOF or GS-331007. Dose linearity of SOF using the PK data from a single therapeutic (400 mg) and supratherapeutic (1200 mg) doses of SOF in fasted healthy subjects and from a single dose of SOF (200 mg) in fasted healthy subjects indicated that near-dose linearity was observed for SOF AUC_{inf} and C_{max}, and GS-331007 AUC_{inf}; GS-331007 C_{max} showed modestly less than dose proportional increases.

5.2.5. Sofosbuvir Pharmacokinetics in HCV-Infected Patients

Cumulatively, the Phase 2 studies evaluated the PK after multiple-dose administration of SOF (100 to 400 mg) in patients with HCV infection under a variety of treatment regimens including monotherapy or combination with RBV with and without Peg-IFN (Phase 2 study designs described in Table 16). SOF exhibited time-independent, near-linear PK across the evaluated doses. No unexpected or significant accumulation (≤ 21%) of SOF or GS-331007 was observed following multiple dosing at the 400-mg dose. Similar to SOF, GS-566500 and GS-331007 demonstrated near dose-proportional increases in exposure with increasing dose.

Mean exposure (population PK analyses) of GS-331007 (AUC_{tau} and C_{max}) and SOF (AUC_{tau}) in HCV-infected patients across Phase 3 studies was comparable with exposure values observed in Phase 2 studies. As estimated from population PK analyses, administration of SOF 400 mg resulted in mean plasma AUC_{tau} and C_{max} of GS-331007 of 7200 ng·h/mL and 582 ng/mL, respectively. Mean plasma AUC_{tau} of SOF was 860 ng·h/mL. GS-331007 and SOF PK were comparable across HCV genotypes.

5.2.6. Comparison of Sofosbuvir and GS-331007 Exposures Between Healthy Subjects and HCV-Infected Patients

The population PK-derived GS-331007 and SOF exposures in healthy subjects and HCV-infected patients following multiple-dose administration of SOF 400 mg were evaluated. Based on population PK modeling, mean GS-331007 exposures (AUC_{tau} and C_{max}) observed in HCV-infected patients (n = 986) in Phase 3 studies were lower (39% and 49%, respectively) than observed in healthy subjects (n = 284). Mean SOF AUC_{tau} was higher (36%) in HCV-infected patients (n = 986) in Phase 3 studies compared with healthy subjects (n = 284).

5.2.7. Demographic Effects

Based on population PK modeling, HCV infection status (healthy subjects versus HCV-infected subgroups) and baseline creatinine clearance (calculated by the Cockcroft-Gault equation) were identified as significant covariates for the oral clearance (CL/F) of the renally eliminated GS-331007 metabolite. HCV infection status (healthy subjects versus HCV-infected subgroups) was the only covariate for SOF CL/F as it is not subject to renal excretion. Mean difference in GS-331007 exposure in HCV-infected patients (Phase 3) between the midpoints of the upper and lowest quartile of creatinine clearance was 35% and 26% for AUC_{tau} and C_{max}, respectively. Considering the PK of GS-331007, including dose-response relationships and underlying variability in the population, the difference in GS-331007 exposure due to creatinine clearance was not considered clinically relevant.

Demographic variables such as age, gender, body mass index (BMI), race, and cirrhosis did not influence SOF and GS-331007 exposure in patients with HCV infection.

5.2.8. Renal Impairment

Single-dose PK of SOF in non-HCV-infected subjects with normal renal function; mild, moderate, or severe renal impairment; or ESRD was evaluated.

Table 12 presents the effect of renal impairment on the PK for SOF and its primary metabolite GS-331007. For GS-331007, an increase in exposure with decrease in renal function was expected as GS-331007 is primarily renally eliminated. Hemodialysis was required for the elimination of GS-331007 in subjects with ESRD, with a 4-hour hemodialysis removing approximately 18% of administered dose. However, for SOF, the increase in exposure was unlikely a result of a decrease in renal clearance (CL_r) because renal excretion of SOF is a minor pathway for its elimination (CL/F range, 1.4% to 3.3%).

These results were recapitulated in population-based analyses of HCV-infected patients (Phase 3 studies) that identified creatinine clearance as the statistically significant determinant of CL/F of GS-331007 and not SOF.

Table 12. Effect of Renal Impairment (% Change) on the Pharmacokinetics of Sofosbuvir 400 mg

Change in GLSM PK Parameter	Mild Renal Impairment (eGFR ≥ 50 and ≤ 80 mL/min/1.73 m^2)	Moderate Renal Impairment (eGFR ≥ 30 and < 50 mL/min/1.73m^2)	Severe Renal Impairment (eGFR < 30 mL/min/1.73m^2 and not on dialysis)	ESRD (SOF Administered Prior to Dialysis)	ESRD (SOF Administered After Dialysis)
GS-331007					
AUC_{inf}	↑ 55	↑ 88	↑ 451	↑ 1280	↑ 2070
C_{max}	↑ 28	↑ 10	↑ 34	↑ 10	↑ 80
SOF					
AUC_{inf}	↑ 61	↑ 107	↑ 171	↑ 28	↑ 60
C_{max}	↑ 28	↑ 54	↑ 77	↑ 21	↓ 2

AUC_{inf} = area under the plasma concentration versus time curve extrapolated to infinite time; CI = confidence interval; C_{max} = maximum observed plasma concentration of drug; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease; GLSM = geometric least-squares mean; PK = pharmacokinetic(s)

Note: 90% CI of the GLSM ratio were within (↔) or extended above (↑) boundaries of 70% to 143% for SOF and GS-331007 relative to subjects with normal renal function.

No clinical safety signals have been identified with respect to SOF and GS-331007 exposures. Safety margins calculated relative to exposure from results of toxicology studies are 5.4 to 11.6 for SOF and 1.6 to 3.5 for GS-331007 in subjects with mild and moderate renal impairment. No dose adjustment of SOF is needed for patients with mild to moderate renal impairment.

A significant dose reduction (eg, 2 to 4-fold) of SOF may be necessary to provide GS-331007 exposures in patients with severe renal impairment or ESRD similar to those with mild to moderate renal impairment. The efficacy of a reduced dose of SOF in this population has not been established at this time and will be conducted in a dedicated study to evaluate two doses of SOF (200 and 400 mg) in HCV-infected patients with severe renal impairment or ESRD on hemodialysis which is planned to start in late 2013.

5.2.9. Hepatic Impairment

The multiple-dose PK of GS-331007 and SOF were evaluated in HCV-infected patients with moderate (Child-Pugh-Turcotte [CPT] Classification B) and severe (CPT Classification C) hepatic impairment after administration of SOF 400 mg for 7 days. GS-331007 exposure, specifically AUC_{tau}, was 18% and 9% higher in patients with moderate or severe hepatic impairment, respectively, compared with historical control patients with normal hepatic function.

SOF mean plasma exposure parameters (AUC_{tau} and C_{max}) were similar in patients with moderate or severe hepatic impairment (CPT Classifications B and C, respectively), and were modestly higher (AUC_{tau}: 126% to 143%; C_{max}: 72% to 85%) than those achieved in patients with normal hepatic function.

HCV RNA decline in HCV-infected patients with varying degrees of hepatic impairment was assessed after 7 days of dosing. Of note, SOF provided potent anti-viral activity (> 3.5 log_{10} decline in HCV RNA) in patients with hepatic impairment. Based on PK and PD results from this study, no dose adjustment of SOF 400 mg is recommended in the setting of hepatic impairment.

Patients with mild hepatic impairment (CPT Classification A) were not specifically evaluated in a hepatic impairment study, but were evaluated in Phase 3 studies.

In the Phase 3 program, compensated cirrhotic patients (CPT Classification A; N = 202 [20% of study population]) and non-cirrhotic patients (N = 784) had comparable mean GS-331007 AUC_{tau} (7150 versus 7210 ng·h/mL) and SOF AUC_{tau} (816 vs 871 ng·h/mL). Cirrhosis was also not identified as a relevant covariate based on population PK analyses.

5.2.10. Established and Other Potentially Significant Drug Interactions

SOF exhibits a favorable absorption, distribution, metabolism, and elimination (ADME) profile and is not involved in interactions mediated by metabolic enzymes including CYP. SOF is a substrate of drug transporter Pgp and BCRP, but GS-331007 is not.

5.2.10.1. Sofosbuvir as Victim Drug

Table 13 presents a summary of the drug-drug interaction studies conducted to evaluate the effect of co-administered drugs on the PK of SOF and GS-331007. In agreement with in vitro data, a drug-drug interaction study with the potent Pgp and BCRP inhibitor cyclosporin A (administered at a high dose of 600 mg) resulted in an increase (approximately 4-fold) in SOF exposure. An additional drug-drug interaction study revealed an increase of < 2-fold in SOF exposure with the less potent Pgp inhibitor ritonavir-boosted darunavir. The exposure of the circulating nucleoside metabolite GS-331007 was unchanged in the presence of Pgp and/or BCRP inhibitors.

The increase in SOF exposure following co-administration with high-dose cyclosporin A 600 mg (considered as “worst case scenario”) was not considered clinically significant because of its very low and transient exposure relative to total drug-related material exposure (AUC of SOF increased from approximately 3% with SOF alone to approximately 10% with SOF and cyclosporin A) and change in overall drug related material was less than 10%. With respect to systemic exposure, adequate safety margins (2- to 16-fold) were maintained upon co-administration with high dose cyclosporin A compared with exposures obtained in toxicology studies. As such, dose modification of SOF is not required. The clinical safety and efficacy of SOF in combination with cyclosporin A, administered at clinical doses, in the posttransplantation setting is being evaluated in an ongoing clinical study.

Table 13. Effect of Coadministered Drugs on the Pharmacokinetics of Sofosbuvir and GS-331007 in Healthy Subjects

Change in GLSM PK Parameter	Cyclosporin A		Tacrolimus		Methadone			
					SOF		GS-331007	
	SOF	GS-331007	SOF	GS-331007	Single Dose	Multiple Dose	Single Dose	Multiple Dose
$AUC_{inf\ or\ tau}$	↑353%	↔	↑13%	↔	↔	↑30%	↔	↔
C_{max}	↑154%	↓40%	↓4%	↔	↓15%	↓5%	↔	↓27%
Change in GLSM PK Parameter	**Atripla (EFV/FTC/TDF)**		**Darunavir/ritonavir**		**Raltegravir**		**Rilpivirine**	
	SOF	**GS-331007**	**SOF**	**GS-331007**	**SOF**	**GS-331007**	**SOF**	**GS-331007**
AUC_{inf}	↔	↔	↑34%	↔	↔	↔	↔	↔
C_{max}	↓19%	↓23%	↑45%	↔	↔	↔	↑21%	↔

ARV = anti-retroviral; AUC_{inf} = area under the plasma concentration versus time curve extrapolated to infinite time; AUC_{tau} = area under the plasma concentration versus time curve over the dosing interval; CI = confidence interval; C_{max} = maximum observed plasma concentration of drug; EFV = efavirenz; FTC = emtricitabine; GLSM = geometric least-squares mean; PK = pharmacokinetics; SOF = sofosbuvir; TDF = tenofovir disoproxil fumarate

Note: 90% CI of the GLSM ratio were within (↔), extended above (↑), or extended below (↓) the predetermined equivalence boundaries of 70% to 143% for studies evaluating methadone and HIV ARVs and bioequivalence boundaries of 80% to 125% were used for the study evaluating cyclosporin A and tacrolimus.

Dose modification is not required when SOF is coadministered with cyclosporin A, tacrolimus, methadone, efavirenz, emtricitabine, tenofovir disoproxil fumarate, darunavir, ritonavir, raltegravir, or rilpivirine. Coadministration of SOF 400 mg with zidovudine, lamivudine, and atazanavir is also permitted in an ongoing study in HCV/HIV-co-infected patients.

5.2.10.2. Sofosbuvir as Perpetrator Drug

In vitro studies indicated that SOF, GS-9851, and its metabolites are unlikely to cause drug interactions due to inhibition or induction of CYP enzymes, UGT1A1, or drug transporters.

Table 14 shows that, in agreement with in vitro data, coadministration of SOF 400 mg did not result in clinically significant alterations of the PK of cyclosporin A, tacrolimus, methadone, or HIV anti-retrovirals (ARVs) efavirenz, emtricitabine, tenofovir disoproxil fumarate, darunavir, ritonavir, raltegravir, or rilpivirine.

Table 14. Effect of Sofosbuvir 400 mg on the Pharmacokinetics of Coadministered Drugs in Healthy Subjects

Change in GLSM PK Parameter	Cyclosporin A	Tacrolimus	R-Methadone	S-Methadone
$AUC_{inf\ or\ tau}$	↔	↔	↔	↔
C_{max}	↔	↓27%	↔	↔

Change in GLSM PK Parameter	Efavirenz	Emtricitabine	Tenofovir	Darunavir	Ritonavir	Raltegravir	Rilpivirine
AUC_{tau}	↔	↔	↔	↔	↔	↓27%	↔
C_{max}	↔	↔	↑25%	↔	↔	↓43%	↔
C_{tau}	↔	↔	↔	↔	↔	↔	↔

ARV = anti-retroviral; AUC_{inf} = area under the plasma concentration versus time curve extrapolated to infinite time; AUC_{tau} = area under the plasma concentration versus time curve over the dosing interval; CI = confidence interval; C_{max} = maximum observed plasma concentration of drug; GLSM = geometric least-squares mean; PK = pharmacokinetics

Note: 90% CI of the GLSM ratio were within (↔), extended above (↑), or extended below (↓) the predetermined equivalence boundaries of 70% to 143% for studies evaluating methadone and HIV ARVs, bioequivalence boundaries of 80% to 125% were used for used the study evaluating cyclosporin A and tacrolimus.

5.2.11. Clinically Important Drug Interactions

Co-administration of SOF with drugs that inhibit Pgp and/or BCRP may increase SOF plasma concentration without increasing GS-331007 plasma concentration. Based on favorable safety profile of SOF over its range of exposures in the broad development program, SOF may be co-administered with Pgp and/or BCRP inhibitors. SOF and GS-331007 are not meaningful inhibitors of Pgp and BCRP and, thus, are not expected to increase exposures of drugs that are substrates of these transporters.

Table 15 summarizes potential important drug interactions for SOF with concomitant medications that are potent Pgp inducers in the intestine (rifampin and St John's Wort) and may significantly decrease SOF plasma concentration leading to reduced therapeutic effect of SOF {23953}, {11178}, {23954}, {23955}. These drug interactions have not been studied in humans. SOF should not be dosed with rifampin or St John's Wort and use with other known inducers of Pgp (eg, carbamazepine and phenytoin) is not recommended. Clinically relevant drug-drug interactions with BCRP substrates and inducers have not been described in the literature, as such, no restrictions are recommended {20200}.

Table 15. Potentially Significant Drug Interaction

Concomitant Drug Class: Drug Name	Clinical Comment
Anti-convulsants: Carbamazepine Phenytoin Phenobarbital Oxcarbazepine	Co-administration of SOF with carbamazepine, phenytoin, phenobarbital, or oxcarbazepine is expected to decrease the concentration of SOF, due to potential induction of Pgp. This may result in a reduced therapeutic effect. Such co-administration is not recommended.
Anti-mycobacterials: Rifampin Rifabutin Rifapentine	Co-administration of SOF with rifabutin or rifapentine is expected to decrease the concentration of SOF, due to potential induction of Pgp. This may result in a reduced therapeutic effect. Such co-administration is not recommended. SOF should not be used with rifampin, a potent intestinal Pgp inducer.
Anti-retrovirals: Tipranavir/ritonavir	Co-administration of SOF with ritonavir-boosted tipranavir is expected to decrease the concentration of SOF, due to potential induction of Pgp. This may result in a reduced therapeutic effect. Such co-administration is not recommended.
Herbal Supplements: St John's Wort	SOF should not be used with St John's Wort, a potent intestinal Pgp inducer.

↓ = decrease; Pgp = p-glycoprotein; SOF = sofosbuvir
Note: This table is not all inclusive

5.3. Clinical Pharmacokinetics/Pharmacodynamics

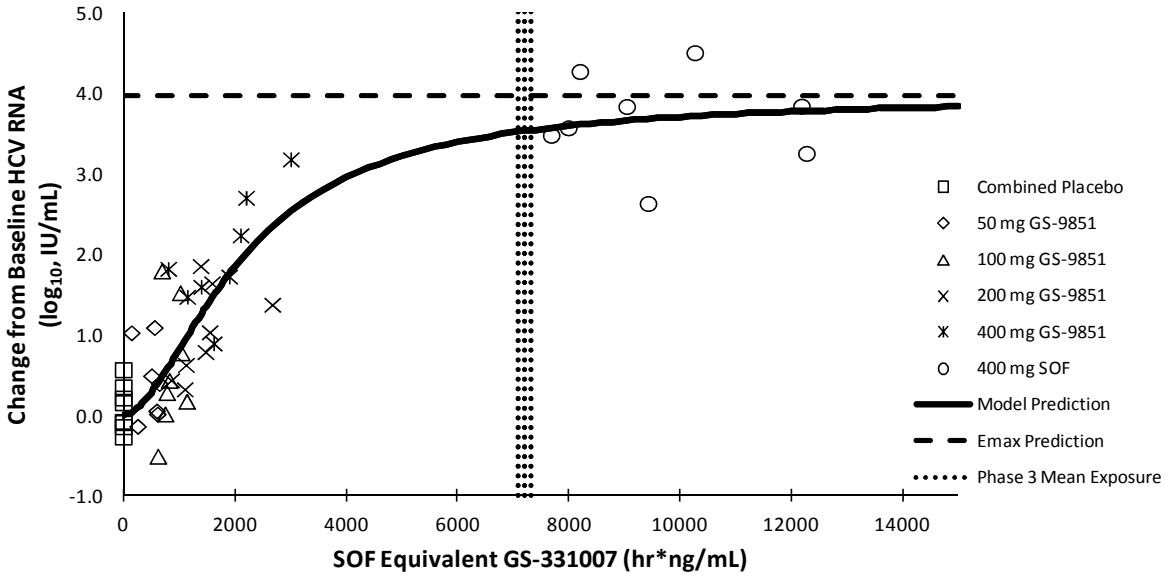
5.3.1. Dose Response Relationship with Efficacy Evaluated as On-Treatment Suppression of HCV RNA

Following administration of SOF or GS-9851 (which contains SOF and the diastereomer in a 1:1 ratio), the common metabolite GS-331007 constituted the majority of systemic exposure; therefore, GS-331007 was used as a surrogate for SOF in exploring exposure-virologic response relationships.

In Phase 1 and 2 clinical studies, pharmacokinetic/pharmacodynamic (PK/PD) relationships for efficacy were examined under two treatment paradigms in patients with genotype 1 HCV infection: SOF/GS-9851 monotherapy (GS-9851 50, 100, 200 and 400 mg once daily with placebo control and SOF 400 mg once daily) and SOF+Peg-IFN+RBV combination therapy (SOF+Peg-IFN+RBV 100, 200, and 400 mg once daily with Peg-IFN+RBV control). Change from baseline in HCV RNA (log_{10} IU/mL) was evaluated after 3 days of monotherapy and SOF+Peg-IFN+RBV therapy.

Figure 3 shows the exposure-response relationship identified for GS-331007 $AUC_{tau,}$ which was best described with a sigmoid E_{max} model. The vertical dotted line is the Phase 3 mean (90% confidence interval [CI]) exposure of GS-331007 from the Phase 3 population PK analyses, the horizontal dashed line is the model estimate of E_{max}, and the solid line is the best fit model (sigmoidal) predicted exposure-response curve. At the mean Phase 3 GS-331007 exposure, the model predicted percent of maximum viral load log_{10} reduction (% of E_{max}) was approximately 90%. GS-331007 exposures in Phase 3 studies reside in the plateau range of this relationship indicating near maximal anti-viral activity.

Figure 3. Relationship Between GS-331007 AUC_{tau} (from Sofosbuvir) and Change from Baseline HCV RNA During Sofosbuvir or GS-9851 Monotherapy After 3 Days of Treatment



HCV = hepatitis C virus; RNA = ribonucleic acid; SOF = sofosbuvir

Note: SOF equivalent GS-331007 AUC estimated as one-half of GS-331007 AUC after administration of the GS-9851, diastereoisomeric mixture (1:1) of SOF and GS-491241. SOF and GS-491241 exhibited differential anti-viral potency; GS-491241 anti-viral activity was 6 to 8-fold lower than SOF; however, both resulted in formation of GS-331007 as the end metabolic product. For exploring GS-331007 exposure-response relationships it was assumed that GS-331007 derived from GS-491241 did not meaningfully contribute to anti-viral activity; accordingly, GS-331007 exposure was corrected to reflect SOF dose administered with the diastereomeric mixture containing SOF.

Model Prediction: $E = (E_{max} \times AUC^{\gamma})/(EC_{50}^{\gamma} + AUC^{\gamma}) = (3.96\ IU/mL \times AUC\ [ng \cdot h/mL]^{1.75})/(2170\ [ng \cdot h/mL]^{1.75} + AUC\ [ng \cdot h/mL]^{1.75})$.

In the SOF+Peg-IFN+RBV combination therapy paradigm, exposure-virologic response relationships between GS-331007 AUC_{tau} and HCV RNA reduction after three days of treatment is in good agreement with the model predictions from the monotherapy paradigm, with the model predicting 88% of maximal response at the 400 mg dose.

Collectively, data from dose-ranging studies as either monotherapy or combination therapy with Peg-IFN+RBV reveal exposure response relationships that support the 400-mg dose of SOF. These data are further supported by the observation of universal on-treatment viral suppression lack of on-treatment virologic breakthrough and no development of drug resistance in the Phase 3 program.

5.3.2. Efficacy Pharmacokinetics/Pharmacodynamics

The PK/PD analyses of GS-331007 and SOF exposure-efficacy relationships from Phase 3 studies (logistic regression) were performed in patients with chronic genotype 2 or 3 HCV infection administered SOF+RBV and patients with chronic genotype 1, 4, 5 or 6 HCV infection administered SOF+Peg-IFN+RBV. For the PK/PD evaluation, GS-331007 AUC_{tau} was considered the primary PK metric and SVR12 was the primary endpoint for efficacy (SVR12; defined as HCV RNA < lower limit of quantitation [LLOQ], ie, < 25 IU/mL 12 weeks after cessation of study drug).

Pharmacokinetics was statistically significant in most but not all univariate (PK only) PK/PD analyses. Multivariate logistic regression analyses exploring the impact of PK within the context of clinical predictors of efficacy revealed that PK was inconsistently associated with SVR12 rates when included in the assessment of overall predictors of efficacy, presented in the efficacy sections for the individual Phase 3 studies in Sections 6.2.5.1 (FISSION), 6.2.5.2 (POSITRON), 6.2.5.3 (FUSION), and 6.2.6.1 (NEUTRINO).

5.3.3. Safety Pharmacokinetics/Pharmacodynamics

A Phase 1 study evaluating single dose therapeutic (400 mg) and supratherapeutic (1200 mg) doses of SOF on the QTc interval in healthy subjects demonstrated a lack of effect of SOF on prolongation of the QTcF interval (primary PD endpoint) that was consistent with the ICH E14 definition of a negative “thorough QT/QTc study.” No clinically significant changes in ECG or wave morphology with SOF-treated subjects were observed. No relationships between SOF or GS-331007 concentrations and QTc intervals were demonstrated. Additionally, no deaths, serious adverse events (SAEs), study discontinuations due to an AE or clinical laboratory abnormality, clinical laboratory abnormalities, or changes in vital signs or physical examination findings were observed. No AEs occurred in this study that would signal a potential proarrhythmic effect.

The mean exposure of GS-331007 (AUC_{tau} and C_{max}) and SOF (AUC_{tau}) at the supratherapeutic dose (SOF 1200 mg) were 3.8-, 3.6-, and 2.9-fold higher, respectively, than the mean exposure (population PK exposures) achieved in the Phase 3 studies and indicate adequate QTc safety margins for GS-331007 in the event of an overdose or drug-drug interaction.

PK/PD analyses of the GS-331007 and SOF exposure-safety relationships were performed using GS-331007 and SOF exposures derived from population PK modeling of data from the four Phase 3 registration studies (FISSION, POSITRON, FUSION, and NEUTRINO) versus safety parameters that included frequently observed AEs or laboratory abnormalities. These AEs or laboratory abnormalities included fatigue, headache, insomnia, irritability, and nausea and maximum decrease from baseline in hemoglobin.

PK/PD analyses of the GS-331007 and SOF exposure-safety relationships revealed no relevant trends in exposure-safety parameters across all GS-331007 (AUC_{tau} and C_{max}) and SOF (AUC_{tau}) quartiles.

6. EFFICACY

6.1. Phase 2 Clinical Development Program

A Phase 2 clinical program consisting of 5 studies which included 711 patients was conducted to explore dose, duration, and combination regimens of SOF and RBV with or without Peg-IFN. Table 16 summarizes the study design and patient populations in the Phase 2 clinical studies.

Table 16. Overview of Phase 2 Clinical Studies in the Sofosbuvir Clinical Program

Study Number	Study Design	Treatment Regimens[a]	Patient Population			
			N[a]	Genotype	Prior HCV Treatment	Cirrhosis Status
P7977-0221	Double-blind, randomized, placebo-controlled, multicenter	SOF 100, 200, or 400 mg or placebo once daily +Peg-IFN+RBV for 28 days followed by Peg-IFN+RBV for 44 weeks	63	1	TN	No patients had cirrhosis.
PROTON (P7977-0422)	Double-blind, randomized, placebo-controlled, multicenter	SOF 200 or 400 mg or placebo once daily +Peg-IFN+RBV for 12 weeks followed by Peg-IFN+RBV for 0 to 36 weeks	146	1, 2, or 3	TN	No patients had cirrhosis.
ELECTRON (P7977-0523)	Open-label, multicenter	SOF+RBV for 12 weeks with and without Peg-IFN (0, 4, 8, or 12 weeks); SOF for 12 weeks; or SOF+Peg-IFN+RBV for 8 weeks	120	1, 2, or 3	TN/TE	No patients had cirrhosis.
ATOMIC (P7977-0724)	Open-label, randomized, multicenter	SOF+Peg-IFN+RBV for 12 or 24 weeks followed by SOF or SOF+RBV for 12 additional weeks in a subset of patients who received SOF+Peg-IFN+RBV for 12 weeks	332	1, 4, 5, 6, or indeterminate[b]	TN	No patients had cirrhosis.
QUANTUM (P2938-0721) (Groups C and G)	Blinded, randomized, multicenter	SOF+RBV for 12 or 24 weeks	50	1, 2, 3, 4, 5, or 6	TN	6% of patients had cirrhosis.

HCV = hepatitis C virus; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; TE = treatment-experienced; TN = treatment-naive

Note: Only treatment regimens and patient populations in the Phase 2 studies that are included to the regulatory submission are included. Unless otherwise indicated, the dose of SOF was 400 mg once daily, the dose of RBV was 1000 or 1200 mg/day (for patients who weighed < 75 kg, the dose of RBV was 1000 mg/day in 2 divided doses and for patients who weighed ≥ 75 kg, the RBV dose was 1200 mg/day in 2 divided doses), and the dose of Peg-IFN was 180 µg weekly.

a Patients received at least one dose of study drug.

b In the ATOMIC study, no patients with chronic genotype 5 or indeterminate genotype HCV infection were enrolled.

c In Groups C and G in the QUANTUM study, no patients with chronic genotype 4, 5, or 6 HCV infection were enrolled.

In the Phase 2 studies, patients received SOF 100, 200, or 400 mg or placebo once daily in combination with RBV (Ribasphere®, Copegus®, or generic) 1000 or 1200 mg orally daily (divided dose) based on weight with or without Peg-IFN (Pegasys®) 180 µg subcutaneously once weekly {24700}, {21450}, {24149}, {26323}. All efficacy analyses were conducted for randomized or enrolled patients who received at least one dose of study drug.

6.1.1. Phase 2 Dose-Finding Studies

Table 17 summarizes the SVR rates for the two dose-finding studies, Study P7977-0221 and the PROTON study. Study P7977-0221 compared SOF 100, 200, and 400 mg once daily or placebo administered orally for 28 days in combination with Peg-IFN+RBV followed by 44 weeks of Peg-IFN+RBV alone in treatment-naive, non-cirrhotic patients with genotype 1 HCV infection. The key efficacy endpoint was rapid virologic response (RVR) defined as the proportion of patients below the lower limit of detection (15 IU/mL) after 4 weeks of treatment. In the three SOF-containing groups, 88% to 94% of patients achieved RVR compared with 21% of patients in the control Peg-IFN+RBV group. When the rate of HCV RNA decline was assessed, the SOF 100 mg+Peg-IFN+RBV group had a slower rate of HCV RNA decline compared with the SOF 200 mg+Peg-IFN+RBV and SOF 400 mg+Peg-IFN+RBV groups. Based on the lower rates of virologic failure following the cessation of SOF in the SOF 200 mg+Peg-IFN+RBV and SOF 400 mg+Peg-IFN+RBV groups compared with the SOF 100 mg+Peg-IFN+RBV group, 200 and 400 mg were the therapeutic doses selected for further evaluation.

Table 17. SVR Rates for Dose-Finding Regimens in Phase 2 Dosing-Finding Studies in Sofosbuvir Clinical Program

Study	Enrolled Genotype	Prior HCV Treatment	Treatment Regimen	N	RVR %	SVR[a] %
P7977-0221	1	TN	SOF 100 mg+Peg-IFN+RBV 28 days→Peg-IFN+RBV 44 weeks	16	88%	56%
			SOF 200 mg+Peg-IFN+RBV 28 days→Peg-IFN+RBV 44 weeks	18	94%	83%
			SOF 400 mg+Peg-IFN+RBV 28 days→Peg-IFN+RBV 44 weeks	15	93%	80%
			placebo+Peg-IFN+RBV 28 days→Peg-IFN+RBV 44 weeks	14	21%	43%
PROTON	1	TN	SOF 200 mg+Peg-IFN+RBV 12 weeks→Peg-IFN+RBV 12 or 36 weeks[b]	48	98%	90%
			SOF 400 mg+Peg-IFN+RBV 12 weeks→Peg-IFN+RBV 12 or 36 weeks[b]	47	98%	91%
			placebo+Peg-IFN+RBV 48 weeks[c]	26	19%	58%

HCV = hepatitis C virus; Peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; RVR= rapid virologic response; SOF = sofosbuvir; SVR = sustained virologic response; SVR24 = sustained virologic response 24 weeks after cessation of study drug; ; TE = treatment-experienced; TN = treatment-naive

Note: Unless otherwise indicated, the dose of SOF was 400 mg once daily, the dose of RBV was 1000 or 1200 mg/day (for patients who weighed < 75 kg, the dose of RBV was 1000 mg/day in 2 divided doses and for patients who weighed ≥ 75 kg, the RBV dose was 1200 mg/day in 2 divided doses), and the dose of Peg-IFN was 180 µg weekly.

a In the P7977-0221 and PROTON studies, SVR24 is presented.

b In the PROTON study, patients received SOF 200 or 400 mg or placebo once daily plus Peg-IFN+RBV for 12 weeks. Patients then received Peg-IFN+RBV for additional 12 or 36 weeks, depending on extended rapid virologic response (defined as undetected HCV RNA at Week 4 and maintained through Week 12).

The PROTON study was designed to assess a longer duration of SOF (12 weeks) to differentiate between the 200- and 400-mg doses. In this study, 95 treatment-naive, non-cirrhotic patients with genotype 1 HCV infection received SOF 200 or 400 mg once daily in combination with Peg-IFN+RBV for 12 weeks, followed by an additional 12 or 36 weeks of Peg-IFN+RBV. Overall, ≥ 90% of the patients receiving SOF achieved SVR24 compared with 58% of patients receiving Peg-IFN+RBV. In this study, three patients had on-treatment virologic failure in the SOF 200 mg+Peg-IFN+RBV group, but no patients had on-treatment virologic failure in the SOF 400 mg+Peg-IFN+RBV group during the second 12-week phase of the study when only Peg-IFN+RBV were being administered after cessation of SOF. These data suggested that the SOF 400 mg dose provided more pronounced viral suppression leading to a lower rate of virologic failure; therefore, the 400-mg dose was selected for evaluation in the Phase 3 clinical studies.

6.1.2. Phase 2 Studies in Patients with Genotype 2 or 3 HCV Infection

Table 18 summarizes the SVR rates for the Phase 2 clinical studies in patients with genotype 2 or 3 HCV infection. The endpoint used to assess efficacy was SVR (ie, undetected HCV RNA [LLOQ or limit of detection for assay depending on assay] 12 or 24 weeks after the cessation of study drug). The PROTON study included a small cohort of 25 treatment-naive, non-cirrhotic patients with genotype 2 or 3 HCV infection. Patients received SOF 400 mg once daily in combination with Peg-IFN+RBV for 12 weeks, with a resulting SVR24 of 92%. Ten of these patients had genotype 3 HCV infection. Of those ten patients, nine achieved SVR and one was lost to follow-up after the first study visit. These encouraging results supported the initiation of the ELECTRON study.

Table 18. SVR for Phase 2 Clinical Studies in Patients with Genotype 2 or 3 HCV Infection

Study	Enrolled Genotype	Prior HCV Treatment	Treatment Regimen	N	SVR[a] %
PROTON	2, 3	TN	SOF 400 mg+Peg-IFN+RBV 12 weeks	25	92%
ELECTRON	2, 3	TN	SOF 400 mg+RBV 12 weeks	10	100%
			SOF 400 mg+Peg-IFN+RBV 4 weeks/SOF+RBV 8 weeks	9	100%
			SOF 400 mg+Peg-IFN+RBV 8 weeks/SOF+RBV 4 weeks	10	100%
			SOF 400 mg+Peg-IFN+RBV 12 weeks	11	100%
			SOF 400 mg 12 weeks	10	60%
			SOF 400 mg+Peg-IFN + RBV 8 weeks	10	100%
	2, 3	TE	SOF 400 mg+RBV 12 weeks	25	68%
QUANTUM	2, 3	TN	SOF 400 mg+RBV 12 weeks	6	67%
			SOF 400 mg+RBV 24 weeks	6	67%

HCV = hepatitis C virus; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virologic response; SVRxx = sustained virologic response xx weeks after cessation of study drug; TE = treatment-experienced; TN = treatment-naive

Note: Unless otherwise indicated, the dose of SOF was 400 mg once daily, the dose of RBV was 1000 or 1200 mg/day (for patients who weighed < 75 kg, the dose of RBV was 1000 mg/day in 2 divided doses and for patients who weighed ≥ 75 kg, the RBV dose was 1200 mg/day in 2 divided doses), and the dose of Peg-IFN was 180 µg weekly.

a In the PROTON study, SVR24 is presented. In the ELECTRON and QUANTUM studies, SVR12 is presented.

The ELECTRON study evaluated treatment-naive patients with genotype 2 or 3 HCV infection. The study was designed initially to evaluate the minimum duration of Peg-IFN in 40 treatment-naive patients; SOF 400 mg once daily in combination with Peg-IFN+RBV for 12 weeks was compared with SOF 400 mg once daily and RBV for 12 weeks in combination with either 0, 4, or 8 weeks of Peg-IFN. Subsequently, three groups were added: one group evaluated SOF monotherapy for 12 weeks in 10 treatment-naive patients, one group evaluated SOF in combination with Peg-IFN+RBV for 8 weeks in 10 treatment-naive patients, and one group evaluated SOF+RBV treatment for 12 weeks in

25 treatment-experienced patients, a patient population with limited treatment options. In this study, all treatment-naive patients receiving SOF+RBV, regardless of the presence or absence of Peg-IFN in the regimen, achieved SVR12.

SOF monotherapy was less efficacious, with only 60% of patients with genotype 2 or 3 HCV infection achieving SVR12, indicating that RBV should be included in SOF-containing regimens. In treatment-experienced patients receiving SOF+RBV for 12 weeks, the SVR12 rate was 68%, with the SVR rates of 100% (6 of 6 patients) and 58% (11 of 19 patients) for patients with genotypes 2 and 3 HCV infection, respectively. These data from the ELECTRON study provided the support for the selection of the SOF 400 mg plus RBV regimen for the Phase 3 FISSION, POSITRON, and FUSION studies in patients with genotype 2 or 3 HCV infection. Of note, 39 treatment-naive patients with genotype 3 HCV infection across the PROTON and ELECTRON studies were treated with SOF+RBV with any duration of Peg-IFN, with 38 of these patients achieving an SVR.

6.1.3. Phase 2 Studies in Patients with Genotype 1, 4, 5, or 6 HCV Infection

Four Phase 2 studies, PROTON, ELECTRON, QUANTUM, and ATOMIC, evaluated SOF 400 mg for up to 24 weeks in treatment-naive patients with genotype 1, 4, 5, or 6 infection. The ELECTRON and QUANTUM studies assessed the oral combination of SOF+RBV, and the PROTON and ATOMIC studies evaluated the SOF+Peg-IFN+RBV regimen. The endpoint used to assess efficacy was SVR (ie, undetected HCV RNA [LLOQ or limit of detection for assay depending on assay] 12 or 24 weeks after the cessation of study drug).

Table 19 summarizes the SVR rates for the PROTON, ELECTRON, QUANTUM, and ATOMIC studies in patients with genotype 1 HCV infection. The addition of Peg-IFN to SOF+RBV treatment resulted in high and reproducible SVR rates between 90% and 95% in the ATOMIC and PROTON studies compared with variable SVR rates between 47% and 84% with SOF+RBV treatment for treatment-naive patients in the ELECTRON and QUANTUM studies.

Table 19. SVR for Phase 2 Clinical Studies in Patients with Genotype 1, 4, 5, or 6 HCV Infection

Study	Enrolled Genotype	Prior HCV Treatment	Treatment Regimen	N	SVR[a] %
PROTON	1	TN	SOF 200 mg+Peg-IFN+RBV 12 weeks→Peg-IFN+RBV 12 or 36 weeks[b]	48	90%
			SOF 400 mg+Peg-IFN+RBV 12 weeks→Peg-IFN+RBV 12 or 36 weeks[b]	47	91%
			placebo+Peg-IFN+RBV 48 weeks	26	58%
ATOMIC	1	TN	SOF 400 mg+Peg-IFN+RBV 12 weeks	52	90%[c]
	1, 4, 6		SOF 400 mg+Peg-IFN+RBV 24 weeks	125	92%[c]
	1		SOF 400 mg+Peg-IFN+RBV 12 weeks→SOF 12 weeks[d]	75	93%
	1		SOF 400 mg+Peg-IFN+RBV 12 weeks→SOF+RBV 12 weeks[d]	75	95%
ELECTRON	1	Null Responder	SOF 400 mg+RBV 12 weeks	10	10%
	1	TN	SOF 400 mg+RBV 12 weeks	25	84%
QUANTUM	1	TN	SOF 400 mg+RBV 12 weeks	19	53%
			SOF 400 mg+RBV 24 weeks	19	47%

HCV = hepatitis C virus; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR= sustained virologic response; SVRxx = sustained virologic response xx weeks after cessation of study drug; TE = treatment-experienced; TN = treatment-naive

Note: Unless otherwise indicated, the dose of SOF was 400 mg once daily, the dose of RBV was 1000 or 1200 mg/day (for patients who weighed < 75 kg, the dose of RBV was 1000 mg/day in 2 divided doses and for patients who weighed ≥ 75 kg, the RBV dose was 1200 mg/day in 2 divided doses), and the dose of Peg-IFN was 180 µg weekly.

a In the PROTON and ATOMIC studies, SVR24 is presented. In the ELECTRON and QUANTUM studies, SVR12 is presented.

b In the PROTON study, patients received SOF 200 or 400 mg or placebo once daily plus Peg-IFN+RBV for 12 weeks. Patients then received Peg-IFN+RBV for additional 12 or 36 weeks, depending on extended rapid virologic response (defined as undetected HCV RNA at Week 4 and maintained through Week 12).

c The ATOMIC study includes 16 patients with genotype 4 or 6 HCV infection; of these patients, 14 (88%) achieved SVR24. The SVR24 rate was 92% in patients with genotype 1 HCV infection who received SOF+Peg-IFN+RBV for 12 or 24 weeks. Patients with genotype 5 infection were allowed; however, none were enrolled.

d In the ATOMIC study, patients who received SOF+Peg-IFN+RBV for 12 weeks were then re-randomized in a 1:1 ratio to received SOF monotherapy or SOF+RBV treatment for 12 weeks.

The ATOMIC study also evaluated whether a 12-week treatment duration of SOF+Peg-IFN+RBV was adequate or if a 24-week treatment duration of SOF+Peg-IFN+RBV was required to attain the ≥ 90% SVR rate observed in the PROTON study. The study enrolled treatment-naive, non-cirrhotic patients with genotype 1 HCV infection. All patients received 12 weeks of SOF+Peg-IFN+RBV treatment followed by one of the following: no further treatment, an additional 12 weeks of SOF+Peg-IFN+RBV, 12 weeks of SOF monotherapy, or 12 weeks of SOF+RBV (Table 16). The

SOF+Peg-IFN+RBV 24-week treatment group also included 16 patients with genotype 4 or 6 HCV infection.

Treatment with SOF+Peg-IFN+RBV for 12 or 24 weeks in treatment-naive, non-cirrhotic patients with genotype 1 HCV infection resulted in SVR12 rates of ≥ 90%. The extension of the SOF+Peg-IFN+RBV treatment regimen from 12 to 24 weeks did not appear to enhance the SVR rate. Patients with genotype 4 or 6 HCV infection who received the 24 weeks of SOF+Peg-IFN+RBV treatment also achieved very high SVR24 rates (88%). This high rate of SVR in patients with genotype 1 HCV infection, along with the simplicity of the 12-week Peg-IFN-containing regimen, supported initiation of the Phase 3 NEUTRINO study to evaluate SOF+Peg-IFN+RBV treatment for 12 weeks in patients with genotype 1, 4, 5, or 6 HCV infection.

6.1.4. Conclusions from the Phase 2 Studies

The results of the Phase 2 studies supported the following conclusions and formed the basis for the design of the Phase 3 studies:

- Confirmed SOF's potent and rapid suppression of HCV RNA against HCV genotypes 1, 2, 3, 4, and 6
- Established 400 mg once daily as an efficacious dose for SOF
- Showed that HCV genotypes 2 and 3 can be effectively treated with SOF+RBV with or without Peg-IFN
- Showed the addition of Peg-IFN to SOF+RBV increases the response rate for HCV genotypes 1, 4, and 6 and allows the duration of therapy to be decreased to 12 weeks
- Showed that SOF, when used in combination with RBV with and without Peg-IFN, was generally safe and well tolerated

6.2. Phase 3 Clinical Development Program

The Phase 3 clinical development program included four Phase 3 registration studies in 1370 mono-infected patients with chronic HCV infection. The program included three studies in patients with genotype 2 or 3 HCV infection and one study in patients with genotype 1, 4, 5, and 6 HCV infection treated with SOF in combination with RBV with or without Peg-IFN. Overall, these studies evaluated a broad range of patients including treatment-naive patients with genotype 1 through 6 HCV infection as well as treatment-experienced patients with genotype 2 and 3 HCV infection. Each of these studies also included a significant subset (ranging from 16% to 34%) of patients with compensated cirrhosis. In addition, patients with HCV infection awaiting liver transplantation are being studied.

The SOF+RBV regimen in patients with genotype 2 or 3 HCV infection allowed for inclusion of a substantial proportion of patients who historically would have been excluded

from participation in interferon-containing regimens, including patients with relative or absolute contraindications to interferon, patients receiving opiate replacement therapy, a substantial proportion of patients with advanced liver disease, advanced age, and patients with higher BMI.

The three studies in patients with genotype 2 or 3 HCV infection are unique in that each study evaluated a different patient population:

- **Treatment-naive patients (FISSION):** Patients who had not been previously treated for chronic HCV infection. For this patient population, the currently recommended treatment is Peg-IFN+RBV for 24 weeks {13693}.

- **Patients who were interferon intolerant, ineligible, or unwilling to take interferon (POSITRON):** This patient population currently has no treatment option.

- **Treatment-experienced patients (FUSION):** Patients who had previously failed Peg-IFN or interferon plus RBV treatment. The AASLD treatment guidelines do not recommend re-treatment for patients who have failed a course of Peg-IFN+RBV; however, these patients can be re-treated with Peg-IFN+RBV for 48 weeks based on the Peg-IFN+RBV prescribing information {13693}, {24701}.

In addition, the NEUTRINO study (Study GS-US-334-0110) was conducted in treatment-naive patients with genotype 1, 4, 5, or 6 HCV infection who were interferon-eligible. For genotype 1 HCV infection, the currently recommended treatment is a protease inhibitor in combination with Peg-IFN+RBV for 24 to 48 weeks {19759}. For genotype 4 or 6 HCV infection, the currently recommended treatment is Peg-IFN+RBV, and for genotype 5 HCV infection, there is no currently recommended treatment {13693}.

Table 20 summarizes the study design, patient population, and primary results of the Phase 3 studies and the Pre-Transplant study.

Table 20. Overview of Phase 3 Studies and the Pre-Transplant Study in the Sofosbuvir Clinical Program

Study	Study Design	Treatment Regimens[a]	N	Genotype	Prior HCV Treatment	Cirrhosis Status	Primary Endpoint	Primary Results
FISSION (P7977-1231)	Phase 3, randomized, open-label, active- controlled, multicenter	SOF+RBV for 12 weeks or Peg–IFN +RBV 800 mg/day (2 divided doses) for 24 weeks	499[a]	2, 3	TN	20% of patients had cirrhosis.	SVR12	67% vs 67% (SOF+RBV vs Peg-IFN+RBV); noninferiority (-15%) demonstrated (p< 0.001)
POSITRON (GS-US-334-0107)	Phase 3, randomized, double-blind, placebo- controlled, multicenter	SOF+RBV or placebo for 12 weeks	278	2, 3	Intolerant, ineligible, or unwilling to take interferon	16% of patients had cirrhosis.	SVR12	78% vs 0% (SOF+RBV vs placebo); superiority demonstrated (p< 0.001)
FUSION (GS-US-334-0108)	Phase 3, randomized, double-blind, multicenter	SOF+RBV for 12 or 16 weeks	201[a]	2, 3	TE	34% of patients had cirrhosis.	SVR12	50% and 73% (SOF+RBV 12 Weeks and 16 Weeks); superiority demonstrated to 25% historical rate (p< 0.001)
NEUTRINO (GS-US-334-0110)	Phase 3, open-label, multicenter	SOF+ Peg-IFN +RBV for 12 weeks	327	1, 4, 5, 6	TN	17% of patients had cirrhosis.	SVR12	90%; superiority demonstrated to 60% historical rate (p< 0.001)
Pre-Transplant (P7977-2025)	Phase 2, open-label, multicenter	SOF+RBV up to 48 weeks or liver transplantation, whichever came first	61	Any genotype	TN, TE	All patients met the Milan criteria and awaiting liver transplant for HCC.	pTVR	62% (8 of 13 patients)

HCC = hepatocellular carcinoma; HCV = hepatitis C virus; NDA = New Drug Application; Peg-IFN = pegylated interferon; pTVR = posttransplant virologic response 12 weeks after liver transplantation; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug; TE = treatment-experienced; TN = treatment-naive

Note: Unless otherwise indicated, the dose of SOF was 400 mg once daily, the dose of RBV was 1000 or 1200 mg/day (for patients who weighed < 75 kg, the dose of RBV was 1000 mg/day in 2 divided doses and for patients who weighed ≥ 75 kg, the RBV dose was 1200 mg/day in 2 divided doses), and the dose of Peg-IFN was 180 µg weekly.

a In the FISSION and FUSION studies, three and six patients, respectively, were determined to have genotype 2 HCV infection at screening; eight of these patients were shown to have recombinant genotype 1/2 HCV infection upon further sequencing and the other patient was shown to have genotype 1 HCV infection by NS5B sequencing, with further HCV core sequencing ongoing. All nine patients were excluded from analyses performed for the full analysis set.

6.2.1. Study Populations in Phase 3 Registration Studies

The demographic characteristics of the patients enrolled in the Phase 3 registration studies were representative of the target indication population. Both males and females were well represented and consistent with the known distribution of HCV infection (63% and 37%, respectively). The mean BMI was 28 kg/m^2 (range, 17 to 56 kg/m^2) across treatment groups, with no upper limit to BMI specified in any of the studies. The percentage of black patients was low (less than 6%) in the studies of patients with genotype 2 or 3 HCV infection, which is consistent with the known data indicating more black patients have genotype 1 HCV infection {23948}. In comparison, in the NEUTRINO study, which included patients with genotype 1 HCV infection, 17% of patients were black. An effort was made to include investigational sites with black patients in their patient populations and, therefore, the percentage of black patients enrolled in this study was higher than in other Phase 3 HCV studies to date or in aggregate reviews of HCV clinical studies over the last decade {25285}, {24932}, {23408}. The mean age was 51 years (range, 19 to 77 years) as there was no upper limit to age specified in the eligibility criteria of the studies. Consequently, 5% of patients were at least 65 years of age, which provided important data for a growing demographic within the HCV patient population and also represented a higher percentage than has been reported for other recent HCV clinical development programs {25285}, {24932}, {21162}.

The baseline disease characteristics of the population studied were also representative of patients who are likely to be treated with SOF-containing regimens once approved. Most patients had the non-CC (CT or TT) IL28B gene (IL28B) allele (62%), high baseline HCV RNA ≥ 6 log10 IU/mL (68%), and elevated ALT > 1.5 × upper limit of the normal range (ULN) (56%). The percentage of patients with cirrhosis ranged from 16% to 34% with the highest percentage of cirrhotic patients in the FUSION study in this treatment-experienced patient population. This proportion of cirrhotic patients included in the Phase 3 studies is substantially higher than other recent HCV clinical development programs {25285}, {24932}.

The SOF clinical development program is also the first Phase 3 program to include patients who were interferon intolerant, interferon medically ineligible, or unwilling to take interferon, which comprise a large patient population with an unmet medical need.

6.2.2. Study Drug Doses for the Phase 3 Studies

In the Phase 3 registration studies for genotype 2 or 3 HCV infection (FISSION, POSITRON, and FUSION), patients in the SOF+RBV groups received SOF 400 mg orally once daily and RBV (Ribasphere) 1000 or 1200 mg orally daily (divided dose) based on weight. In the Peg-IFN+RBV group in the FISSION study, patients received Peg-IFN (Pegasys) 180 μg subcutaneously once weekly and RBV (Ribasphere) 800 mg orally daily (divided dose) per prescribing recommendations {24700}, {21450}. In the POSITRON study, the placebo group received a matching placebo for SOF orally once daily and a matching placebo for RBV orally twice daily. In the FUSION study, the SOF+RBV 12 Week group received a matching placebo for SOF orally once daily and a matching placebo for RBV orally twice daily from Weeks 12 through 16.

In the Phase 3 registration study for genotype 1, 4, ,5 ,and 6 HCV infection (NEUTRINO), patients received SOF 400 mg orally once daily, Peg-IFN (Pegasys) 180 μg subcutaneously once weekly, and RBV (Ribasphere) orally 1000 or 1200 mg daily (divided dose) based on weight {24700}, {21450}.

6.2.3. Statistical Considerations for the Phase 3 Studies

The goal of treatment for chronic HCV infection is viral eradication. All Phase 3 registration studies used the same primary endpoint, SVR12, defined as an HCV RNA assay result below LLOQ (< 25 IU/mL) using the Cobas Taqman Assay Version 2.0 for use with the High Pure System 12 weeks following the cessation of study drug. All patients who did not have an SVR12 assessment were imputed as failures, unless at both the preceding and subsequent visit, the HCV RNA was < LLOQ.

All four of the studies also included extensive health-related quality-of-life (HRQL) assessments as exploratory endpoints.

For the POSITRON, FUSION, and NEUTRINO studies, all HCV RNA results except at screening were blinded to the sponsor and investigator (except for select employees responsible for selection of virologic samples for sequencing and analyses). HCV RNA was monitored by a third party (Duke Clinical Research Institute) to identify any patients receiving active study drug that met virologic stopping criteria. For the FISSION study, HCV RNA was blinded to the sponsor (except for select employees responsible for selection of virologic samples for sequencing analysis and identification of patients meeting virologic stopping criteria), but not to the investigator.

All demography analyses were conducted with the intent-to-treat analysis set (defined as patients who received at least one dose of study drug). Unless otherwise specified, efficacy analyses were conducted with the full analysis set (defined as patients with the protocol-specified HCV genotypes who were randomized and received at least one dose of study drug). All safety analyses were conducted with the safety analysis set (defined as patients who received at least one dose of study drug).

6.2.3.1. Concordance of SVR 12 and SVR 24 as the Primary Efficacy Endpoint

Concordance of SVR12 and SVR24 in the SOF clinical program was assessed. Patients receiving SOF 400 mg for at least 12 weeks either alone or in combination with RBV or Peg-IFN+RBV were included in the analysis. In the Phase 2 ATOMIC, ELECTRON, and PROTON studies, 547 patients had HCV RNA measured at post-treatment Weeks 12 and 24. One patient with SVR 12 relapsed at post-treatment Week 24, giving a positive predictive value between SVR12 and SVR24 of 99.8%. For the Phase 3 studies, complete SVR24 data are available for the POSITRON study and for patients in the SOF+RBV group in the FISSION study of whom 433 patients were included in the analysis. Two patients with SVR 12 relapsed by post-treatment Week 24, giving a positive predictive value between SVR 12 and SVR 24 of 99.4%. These data were consistent with those observed with Peg-IFN+RBV

therapy and support the use of SVR 12 as the primary efficacy endpoint for treatment with SOF-containing regimens {22617}, {22618}, {22619}.

6.2.4. Primary Efficacy Endpoint for the Phase 3 Studies

In the four Phase 3 studies, the intent-to-treat analysis set was defined as the group of patients who received at least one dose of study drug. The full analysis set was defined as the group of patients with the protocol-specified HCV genotypes who were randomized and received at least one dose of study drug. For the POSITRON and NEUTRINO studies, the intent-to-treat and full analysis sets were identical. However, in the FISSION and FUSION studies, the genotypes of nine patients were misclassified: three patients each in the SOF+RBV group in the FISSION study, SOF+RBV 12 Week group in the FUSION study, and SOF+RBV 16 Week group in the FUSION study. These patients were determined to have genotype 2 HCV infection at screening using by the VERSANT® HCV Genotype INNO-LiPA 2.0 (LiPA) screening assay (n = 8) or the Abbott RealTime HCV Genotype II assay (n = 1), but shown to have genotype 1 HCV infection by NS5B sequencing assay. Eight of these nine patients were shown to have genotype 2 HCV core protein upon further HCV core sequencing. Therefore, these eight patients were infected with recombinant genotype 1/2 HCV with the core from genotype 2 HCV and NS5B from genotype 1 HCV. The remaining patient was determined to have genotype 2 HCV infection at screening, but shown to have genotype 1 HCV infection by NS5B sequencing, with HCV core sequencing analysis ongoing. As a result, these nine patients were excluded from the full analysis set as was pre-specified in the statistical analysis plan.

Table 21 presents the primary efficacy endpoint, SVR12, for the intent-to-treat analysis set and full analysis set in the FISSION, POSITRON, FUSION, and NEUTRINO studies.

Table 21. FISSION, POSITRON, FUSION, and NEUTRINO: SVR12 (Intent-To-Treat and Full Analysis Sets)

Study	Treatment		Intent-To-Treat Analysis Set	Full Analysis Set
FISSION	SOF+RBV 12 Weeks	SVR, n/N (%)	171/256 (67%)	170/253 (67%)[a]
		95% CI	61% to 73%	61% to 73%
	Peg-IFN+RBV 24 Weeks	SVR, n/N (%)	162/243 (67%)	162/243 (67%)
		95% CI	60% to 73%	60% to 73%
POSITRON[b]	SOF+RBV 12 Weeks	SVR, n/N (%)	161/207 (78%)	161/207 (78%)
		95% CI	71% to 83%	71% to 83%
FUSION	SOF+RBV 12 Weeks	SVR, n/N (%)	51/103 (50%)	50/100 (50%)[c]
		95% CI	40% to 60%	40% to 60%
	SOF+RBV 16 Weeks	SVR, n/N (%)	70/98 (71%)	69/95 (73%)[c]
		95% CI	61% to 80%	63% to 81%
NEUTRINO	SOF+Peg-IFN +RBV 12 Weeks	SVR, n/N (%)	295/327 (90%)	295/327 (90%)
		95% CI	86% to 93%	86% to 93%

Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug

a In the FISSION study, three patients in the SOF+RBV group were determined to have genotype 2 HCV infection at screening. Two of these patients were shown to have recombinant genotype 1/2 HCV infection upon further sequencing, and the other patient was shown to have genotype 1 HCV infection by NS5B sequencing, with further HCV core sequencing ongoing. These three patients were excluded from analyses for the full analysis set.

b None of the patients in the placebo group in the POSITRON study achieved SVR12 and results for the placebo group are not included in this table.

c In the FUSION study, three patients each in the SOF+RBV 12 Week and 16 Week groups were determined to have genotype 2 HCV infection at screening, but these patients were shown to have recombinant genotype 1/2 HCV infection upon further sequencing and were excluded from analyses for the full analysis set.

The SVR rates were similar between the intent-to-treat analysis set and full analysis set in each of the four studies and did not change the interpretations. Therefore, unless otherwise specified, the efficacy results for the four Phase 3 studies are presented for the full analysis set in the following sections.

6.2.5. Efficacy of SOF+RBV Treatment in Patients with Chronic Genotype 2 or 3 HCV Infection

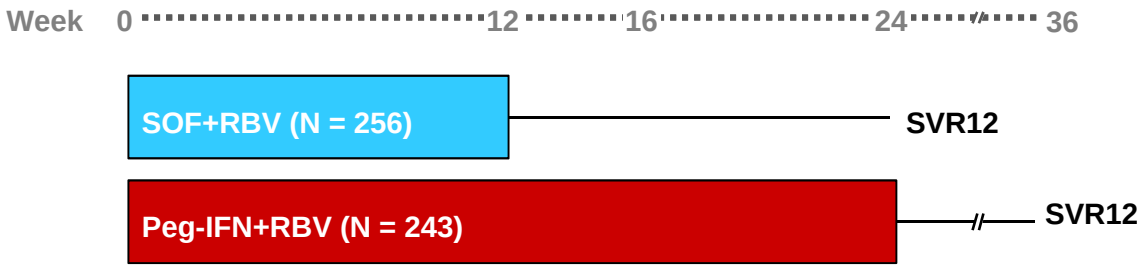
6.2.5.1. FISSION: Treatment-Naive Patients with Chronic Genotype 2 or 3 HCV Infection

FISSION was a Phase 3, multicenter, randomized, open-label, active-controlled study evaluating the efficacy and safety of treatment-naive interferon-eligible patients with genotype 2 or 3 HCV infection. The results of patients who received SOF+RBV treatment for 12 weeks were compared with patients who received Peg-IFN+RBV treatment for

24 weeks. Treatment with Peg-IFN+RBV treatment for 24 weeks was selected for the control group in this study because it is the currently recommended treatment for treatment-naive patients with genotype 2 or 3 HCV infection {13693}.

Figure 4 presents the study design for the FISSION study. Patients were enrolled in a prespecified 3:1 ratio of patients with genotype 2 or genotype 3 HCV infection. Patients were also randomized in a 1:1 ratio (stratified by HCV genotype, screening HCV RNA level [< or ≥ 6 $\log_{10}$ IU/mL], and cirrhosis status) to receive SOF+RBV or Peg-IFN+RBV. Of the 499 patients who were randomized and received at least one dose of study drug, 20% (100 patients) had evidence of cirrhosis at screening.

Figure 4. FISSION: Schema of Study Design



Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug

The primary efficacy analysis assessed noninferiority of the SVR12 of SOF+RBV treatment for 12 weeks versus Peg-IFN+RBV treatment for 24 weeks. A 95% CI for the difference in SVR12 rates of SOF+RBV and Peg-IFN+RBV was constructed based on stratum-adjusted Mantel-Haenszel proportions for the assessment of noninferiority. It was anticipated that SVR12 of SOF+RBV treatment would be similar to that of Peg-IFN+RBV and the SOF+RBV treatment would be better tolerated. A noninferiority margin of 15% was used for SVR12 based on the clinical assessment that eliminating Peg-IFN from the treatment regimen and shortening the duration of treatment from 24 to 12 weeks would result in a substantial benefit to the patient and that a SVR within the 15% noninferiority margin would make SOF+RBV treatment for 12 weeks an attractive alternative treatment for physicians and patients. Superiority would be demonstrated using a 2-sided stratified Cochran-Mantel-Haenszel test stratified by HCV genotype, screening HCV RNA, and cirrhosis status if the 2-sided p-value associated with the test of superiority was < 0.05.

A total of 499 patients were randomized and received at least one dose of study drug: 256 patients in the SOF+RBV group and 243 patients in the Peg-IFN+RBV group. Of these 499 patients, 434 (87%) completed study treatment as planned: 245 patients (96%) in the SOF+RBV group and 189 patients (78%) in the Peg-IFN +RBV group. The difference in the study treatment completion rate was driven predominantly by lower rates of discontinuations due to AEs and virologic failure in the SOF+RBV group (1% and < 1%, respectively) compared with the Peg-IFN+RBV group (11% and 7%, respectively).

Table 22 presents key demographic and baseline disease characteristics. The majority of patients (72%) had genotype 3 HCV infection; 27% of patients had genotype 2 HCV infection. Demographic and baseline disease characteristics were generally balanced across both treatment groups.

Table 22. FISSION: Key Demographic and Disease Baseline Characteristics

	FISSION	
	SOF+RBV 12 Weeks	**Peg-IFN +RBV 24 Weeks**
	N = 256	**N = 243**
Mean age (range), years	48 (20, 72)	48 (19, 77)
Male, n (%)	171 (67%)	156 (64%)
White, n (%)	223 (87%)	212 (87%)
Mean BMI (range), kg/m^2	28 (17, 51)	28 (19, 52)
IL28B CC allele, n (%)	108 (43%)	106 (44%)
Genotype 3, n (%)	183 (72%)	176 (72%)
Mean Baseline HCV RNA (range), log_{10} IU/mL	6.0 (3.2, 8.3)	6.0 (3.2, 7.6)
Cirrhosis, n (%)	50 (20%)	50 (21%)

BMI = body mass index; HCV = hepatitis C virus; Peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir

Table 23 summarizes SVR12 overall and by HCV genotype and other key subgroups in the FISSION study. The forest plot and CIs for the subgroup analyses are provided in Appendix 3. The primary efficacy endpoint of noninferiority was met for 12 weeks of SOF+RBV compared with 24 weeks of Peg-IFN+RBV, with 67% (170 of 253 patients; 95% CI: 61% to 73%) of patients achieving SVR12 in the SOF+RBV treatment group versus 67% (162 of 243 patients; 95% CI: 60% to 73%) in the Peg-IFN+RBV treatment group.

In the SOF+RBV group, 83 of 253 patients (33%) did not achieve SVR: 30% (74 of 249 patients with HCV RNA < LLOQ at end of treatment) relapsed, < 1% (1 of 253 patients) had on-treatment virologic failure likely due to non-compliance, and 3% (8 of 253 patients) did not have SVR12 for reasons other than virologic failure (eg, lost to follow-up or withdrew consent). For the Peg-IFN+RBV group, 33% of patients (81 of 243 patients) did not achieve SVR12: 21% (46 of 217 patients with HCV RNA < LLOQ at end of treatment) relapsed, 7% (18 of 243 patients) had on-treatment virologic failure, and 7% (17 of 243 patients) did not have SVR12 for reasons other than virologic failure.

Subgroup analyses were generally similar for SVR12 rates between the treatment groups for age, sex, race, ethnicity, baseline BMI, IL28B genotype, and baseline HCV RNA. In both treatment groups, patients with genotype 2 HCV infection had higher SVR12 rates than patients with genotype 3 HCV infection. Non-cirrhotic patients also had higher SVR12 rates than cirrhotic patients in both treatment groups. For the SOF+RBV treatment group, a

multivariate logistic regression analysis showed that HCV genotype 2 ($p < 0.001$) and the absence of cirrhosis ($p = 0.005$) were strongly associated with a higher SVR rate. Drug exposure (GS 331007 AUC_{tau}) did not demonstrate a statistically significant relationship on SVR12 rates in patients with genotype 2 or 3 HCV infection.

Table 23. FISSION: SVR12 Overall and by Key Subgroups

	FISSION					
	Genotype 2/3		Genotype 2		Genotype 3	
	SOF+RBV 12 Weeks	Peg-IFN+RBV 24 Weeks	SOF+RBV 12 Weeks	Peg-IFN+RBV 24 Weeks	SOF+RBV 12 Weeks	Peg-IFN+RBV 24 Weeks
	N = 253 n/N (%)	N = 243 n/N (%)	N = 70 n/N (%)	N = 67 n/N (%)	N = 183 n/N (%)	N = 176 n/N (%)
Overall	170/253 (67%)[a,b]	162/243 (67%) [a,b]	68/70 (97%)	52/67 (78%)	102/183 (56%)	110/176 (63%)
95% CI	61% to 73%	60% to 73%	90% to 100%	66% to 87%	48% to 63%	55% to 70%
Cirrhosis Status						
No Cirrhosis	147/204 (72%)	143/193 (74%)	58/59 (98%)	44/54 (81%)	89/145 (61%)	99/139 (71%)
Cirrhosis	23/49 (47%)	19/50 (38%)	10/11 (91%)	8/13 (62%)	13/38 (34%)	11/37 (30%)
IL28B Genotype						
CC	74/106 (70%)	82/106 (77%)	31/31 (100%)	28/34 (82%)	43/75 (57%)	54/72 (75%)
Non-CC	96/145 (66%)	79/136 (58%)	37/39 (95%)	24/33 (73%)	59/106 (56%)	55/103 (53%)
Baseline HCV RNA						
$< 6 \log_{10}$ IU/mL	80/107 (75%)	71/106 (67%)	24/24 (100%)	17/23 (74%)	56/83 (67%)	54/83 (65%)
$\geq 6 \log_{10}$ IU/mL	90/146 (62%)	91/137 (66%)	44/46 (96%)	35/44 (80%)	46/100 (46%)	56/93 (60%)
Age at Baseline						
< 50 years	80/126 (63%)	86/118 (73%)	22/22 (100%)	14/18 (78%)	58/104 (56%)	72/100 (72%)
≥ 50 years	90/127 (71%)	76/125 (61%)	46/48 (96%)	38/49 (78%)	44/79 (56%)	38/76 (50%)
Sex						
Male	103/168 (61%)	96/156 (62%)	42/43 (98%)	27/39 (69%)	61/125 (49%)	69/117 (59%)
Female	67/85 (79%)	66/87 (76%)	26/27 (96%)	25/28 (89%)	41/58 (71%)	41/59 (69%)

	FISSION					
	Genotype 2/3		Genotype 2		Genotype 3	
	SOF+RBV 12 Weeks	Peg-IFN+RBV 24 Weeks	SOF+RBV 12 Weeks	Peg-IFN+RBV 24 Weeks	SOF+RBV 12 Weeks	Peg-IFN+RBV 24 Weeks
	N = 253 n/N (%)	N = 243 n/N (%)	N = 70 n/N (%)	N = 67 n/N (%)	N = 183 n/N (%)	N = 176 n/N (%)
Race						
Black	9/12 (75%)	2/5 (40%)	3/4 (75%)	1/2 (50%)	6/8 (75%)	1/3 (33%)
Non-Black	161/241 (67%)	160/238 (67%)	65/66 (98%)	51/65 (78%)	96/175 (55%)	109/173 (63%)
Ethnicity						
Hispanic or Latino	29/40 (73%)	20/31 (65%)	15/16 (94%)	6/9 (67%)	14/24 (58%)	14/22 (64%)
Not Hispanic or Latino	141/213 (66%)	142/212 (67%)	53/54 (98%)	46/58 (79%)	88/159 (55%)	96/154 (62%)
Baseline BMI						
< 30 kg/m^2	120/176 (68%)	117/172 (68%)	50/50 (100%)	35/45 (78%)	70/126 (56%)	82/127 (65%)
≥ 30 kg/m^2	50/77 (65%)	45/71 (63%)	18/20 (90%)	17/22 (77%)	32/57 (56%)	28/49 (57%)

BMI = body mass index; CI = confidence interval; HCV = hepatitis C virus; Peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug

Note: Three patients in the SOF+RBV group were determined to have genotype 2 HCV infection at screening. Two of these patients were shown to have recombinant genotype 1/2 HCV infection upon further sequencing, and the other patient was shown to have genotype 1 HCV infection by NS5B sequencing, with further HCV core sequencing ongoing. These three patients were excluded from analyses for the full analysis set.

Note: The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.

a The stratum-adjusted difference in the proportions was 0.3% [95% CI: –7.5% to 8.0%]; the lower bound of the 2-sided 95% CI on the difference in SVR12 rates [ie, SOF+RBV group − Peg-IFN+RBV group] was > –15%. Superiority of SOF+RBV over Peg-IFN+RBV was not demonstrated (p = 0.94, Cochran-Mantel-Haenszel test stratified by HCV genotype, screening HCV RNA, and cirrhosis status).

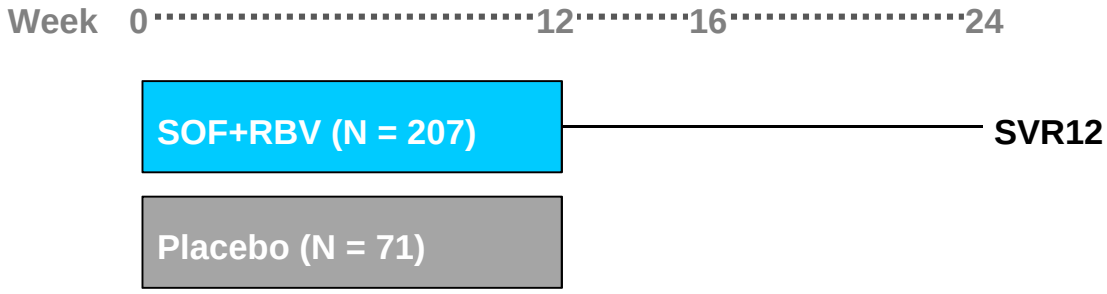
b Non-inferiority of SOF+RBV versus Peg-IFN+RBV was demonstrated (p < 0.001; one-sided p-value based on stratum-adjusted Mantel-Haenszel proportions).

6.2.5.2. POSITRON: Patients With Chronic Genotype 2 or 3 HCV Infection Who Were Interferon Intolerant, Interferon Ineligible, or Unwilling to Take Interferon

POSITRON was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of SOF+RBV treatment for 12 weeks compared with placebo in patients with chronic genotype 2 or 3 HCV infection who were interferon intolerant, interferon ineligible (medical conditions precluding interferon therapy), or unwilling to take interferon. There is no current approved treatment available for HCV-infected patients with these characteristics; therefore, a placebo group was included to allow a comparison of safety and tolerability and quality of life assessments with SOF+RBV treatment. All patients who received placebo were offered SOF+RBV treatment at the end of the study.

Figure 5 presents the study design for the POSITRON study. Patients were randomized in a 3:1 ratio (stratified by cirrhosis status) to receive SOF+RBV or placebo. Of the 278 patients who were randomized and received at least one dose of study drug, 16% (44 patients) had evidence of cirrhosis at screening. The primary efficacy analysis assessed the superiority of SOF+RBV treatment for 12 weeks compared with placebo. The difference in SVR12 rates between treatment groups and associated 95% CIs were calculated based on stratum-adjusted Mantel-Haenszel proportions. Superiority was demonstrated if the two-sided Cochran-Mantel-Haenszel p-value associated with the test of superiority was < 0.05.

Figure 5. POSITRON: Schema of Study Design



RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug

A total of 278 patients were randomized and received at least one dose of study drug: 207 patients in the SOF+RBV group and 71 patients in the placebo group. Of these patients, 201 patients in the SOF+RBV group and 68 patients in the placebo group completed study treatment as planned. A total of 3% of patients (9 patients) prematurely discontinued study drug (6 patients [3%] in the SOF+RBV group and 3 patients [4%] in the placebo group).

Table 24 presents key demographic and baseline disease characteristics. Demographic and baseline disease characteristics were generally balanced across both treatment groups.

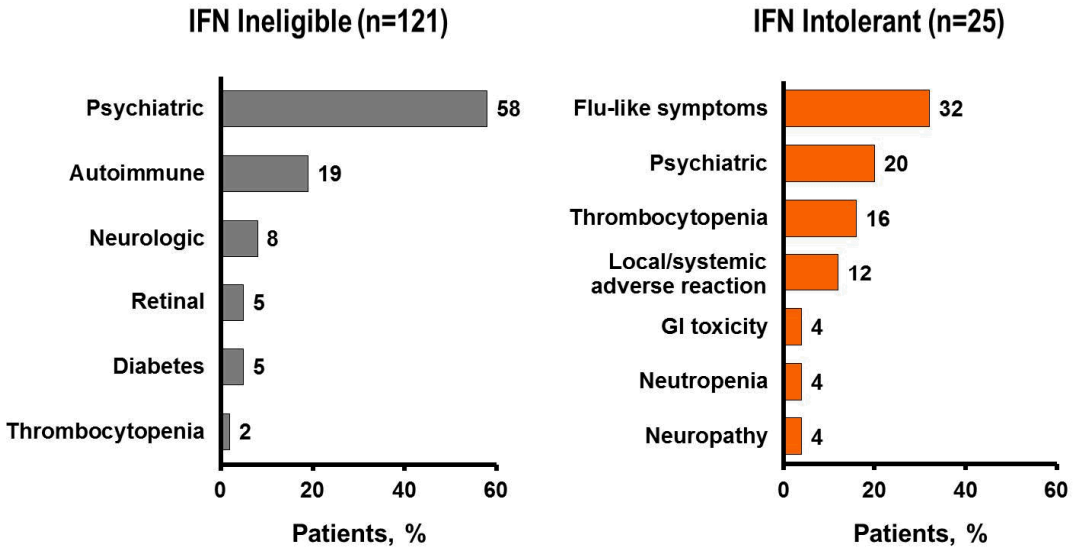
Table 24. POSITRON: Key Demographic and Disease Baseline Characteristics

	POSITRON	
	SOF+RBV 12 Weeks	**Placebo 12 Weeks**
	N = 207	**N = 71**
Mean age (range), years	52 (21, 75)	52 (28, 67)
Male, n (%)	117 (57%)	34 (48%)
White, n (%)	188 (91%)	66 (93%)
Mean BMI (range), kg/m^2	28 (18, 53)	28 (20, 43)
IL28B CC allele, n (%)	97 (47%)	29 (41%)
Genotype 2, n (%)	109 (53%)	34 (48%)
Mean Baseline HCV RNA (range), log_{10} IU/mL	6.3 (3.2, 7.5)	6.3 (3.7, 7.6)
Cirrhosis, n (%)	31 (15%)	13 (18%)
Interferon Unwilling, n (%)	102 (49%)	30 (42%)
Interferon Ineligible, n (%)	88 (43%)	33 (46%)
Interferon Intolerant, n (%)	17 (8%)	8 (11%)

BMI = body mass index; HCV = hepatitis C virus; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir

Figure 6 presents the reasons for interferon ineligibility and interferon intolerance.

Figure 6. POSITRON: Reasons for Interferon Ineligibility and Interferon Intolerance



GI = gastrointestinal; IFN = interferon

Table 25 summarizes SVR12 overall and by HCV genotype and other key subgroups in the POSITRON study. The SVR rates are shown for the SOF+RBV group only since no patients in the placebo group achieved an SVR. The forest plot and CIs for the subgroup analyses are provided in Appendix 2. The primary efficacy endpoint of superiority was met for 12 weeks of SOF+RBV compared with placebo, with 78% of patients with genotype 2 or 3 HCV infection achieving SVR12 in the SOF+RBV treatment group versus 0% in the placebo group ($p < 0.001$). In the SOF+RBV group, 22% of patients (46 of 207 patients) did not achieve SVR12: 20% (42 of 205 patients with HCV RNA < LLOQ at end of treatment) relapsed and 2% (4 of 207 patients) did not have SVR12 for reasons other than virologic failure (eg, lost to follow-up or withdrew consent). In the placebo group, no patient had undetectable HCV RNA during or at the end of treatment.

Patients with genotype 2 HCV infection had higher SVR12 rates than patients with genotype 3 HCV infection. Non-cirrhotic patients also had higher SVR12 rates than cirrhotic patients. The difference in SVR12 rates in cirrhotic patients compared with non-cirrhotic patients was attributable to differences in patients with genotype 3 HCV infection; cirrhotic and non-cirrhotic patients with genotype 2 HCV infection achieved similarly high rates of SVR12 (94% and 92%, respectively). A multivariate logistic regression analysis showed that HCV genotype 2 was significantly associated with higher SVR rates (p-value < 0.001). Drug exposure (GS-331007 AUC_{tau}) was assessed and determined to have a statistically significant relationship on SVR12 rates in patients with genotype 3 HCV infection with no evidence for an exposure-efficacy relationship in patients with genotype 2 HCV infection.

Table 25. POSITRON: SVR12 Overall and by Key Subgroup

	POSITRON		
	Genotype 2/3	Genotype 2	Genotype 3
	SOF+RBV 12 Weeks		
	N = 207 n/N (%)	N = 109 n/N (%)	N = 98 n/N (%)
Overall	**161/207 (78%)**	**101/109 (93%)**	**60/98 (61%)**
95% CI	71% to 83%	86% to 97%	51% to 71%
Interferon Classification			
Ineligible	69/88 (78%)	36/41 (88%)	33/47 (70%)
Intolerant	13/17 (76%)	9/9 (100%)	4/8 (50%)
Unwilling	79/102 (77%)	56/59 (95%)	23/43 (53%)
Cirrhosis Status			
No Cirrhosis	142/176 (81%)	85/92 (92%)	57/84 (68%)
Cirrhosis	19/31 (61%)	16/17 (94%)	3/14 (21%)
IL28B Genotype			
CC	74/97 (76%)	40/45 (89%)	34/52 (65%)
Non-CC	87/110 (79%)	61/64 (95%)	26/46 (57%)
Baseline HCV RNA			
< 6 $\log_{10}$ IU/mL	51/67 (76%)	29/33 (88%)	22/34 (65%)
≥ 6 $\log_{10}$ IU/mL	110/140 (79%)	72/76 (95%)	38/64 (59%)
Duration on Prior HCV Treatment			
None	140/170 (82%)	86/93 (92%)	54/77 (70%)
≤ 12 Weeks	15/21 (71%)	11/11 (100%)	4/10 (40%)
> 12 Weeks	6/16 (38%)	4/5 (80%)	2/11 (18%)
Age at Baseline			
< 50 years	53/72 (74%)	27/29 (93%)	26/43 (60%)
≥ 50 years	108/135 (80%)	74/80 (93%)	34/55 (62%)
Sex			
Male	85/117 (73%)	59/64 (92%)	26/53 (49%)
Female	76/90 (84%)	42/45 (93%)	34/45 (76%)
Race			
Black	8/9 (89%)	8/9 (89%)	0/0
Non-Black	153/198 (77%)	93/100 (93%)	60/98 (61%)
Ethnicity			
Hispanic or Latino	14/19 (74%)	9/11 (82%)	5/8 (63%)
Not Hispanic or Latino	147/188 (78%)	92/98 (94%)	55/90 (61%)
Baseline BMI			
< 30 kg/m^2	103/136 (76%)	61/66 (92%)	42/70 (60%)
≥ 30 kg/m^2	58/71 (82%)	40/43 (93%)	18/28 (64%)

BMI = body mass index; CI = confidence interval; HCV = hepatitis C virus; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug

Note: The response rate for the placebo group was zero and was not included in this table.

Note: The exact 95% CI for the proportion within treatment group was based on the Clopper-Pearson method.

Note: The primary efficacy endpoint of superiority was met for 12 weeks of SOF+RBV compared with placebo, with 78% (95% CI: 71% to 83%) of patients with genotype 2 or 3 HCV infection achieving SVR12 in the SOF+RBV treatment group versus 0% (95% CI: 0.0% to 5%) in the placebo group ($p < 0.001$).

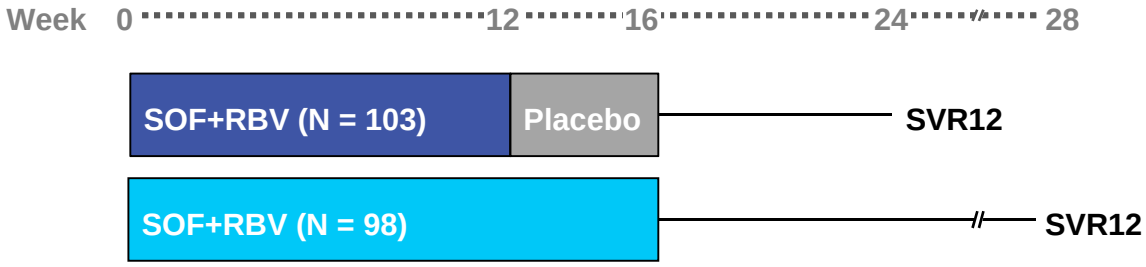
6.2.5.3. FUSION: Treatment-Experienced Patients with Chronic Genotype 2 or 3 HCV Infection

FUSION was a Phase 3, multicenter, randomized, double-blind study evaluating the efficacy and safety of SOF+RBV treatment for 12 or 16 weeks in patients with chronic genotype 2 or 3 HCV infection who have failed prior treatment with an interferon-based regimen. The treatment-experienced genotype 2 or 3 population was selected for this study because of the limited treatment options available to this patient population. The AASLD treatment guidelines do not recommend re-treatment for patients who have failed a course of Peg-IFN+RBV; however, these patients can be re-treated with Peg-IFN+RBV for 48 weeks based on the Peg-IFN+RBV prescribing information {13693}, {24701}.

A SOF+RBV group with a 16-week duration was included in the study to evaluate whether a longer duration would lead to improved response rates compared with a 12-week duration in this difficult-to-treat population.

Figure 7 presents the study design for the FUSION study. Patients were randomized 1:1 (stratified by HCV genotype and cirrhosis status) to receive 12 weeks of SOF+RBV followed by 4 weeks of SOF placebo and RBV placebo or 16 weeks of SOF+RBV treatment. Of the 201 patients who were randomized and received at least one dose of study drug, 34% (68 patients) had evidence of cirrhosis at screening.

Figure 7. FUSION: Schema of Study Design



RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug

Since re-treatment with Peg-IFN+RBV is not recommended for this patient population, a historical control SVR rate was used to assess the efficacy of the SOF+RBV regimen. The two primary statistical hypotheses of this study were that the SVR12 rates in both treatment groups were higher than a null rate of 25%. The 25% SVR null rate was derived from SVR rates from the EPIC study for patients with genotype 2 or 3 HCV infection and an expected improved safety profile and shorter duration of treatment {17114}.

Both hypotheses were tested at a significance level of 0.025 using a Bonferroni correction to adjust for multiple testing. The 2-sided 95% exact CI based on the Clopper-Pearson method was calculated for the SVR12 rate in each of the two treatment groups and the two-sided 95% CI of the difference in SVR12 rates between the two treatment groups (SOF+RBV

12 Week group – SOF+RBV 16 Week group) was constructed based on stratum-adjusted Mantel-Haenszel proportions.

A total of 201 patients were randomized and received at least one dose of study drug: 103 patients in the SOF+RBV 12 Week group and 98 patients in the SOF+RBV 16 Week group. Of these 201 patients, only one patient prematurely discontinued study drug (during placebo treatment in the SOF+RBV 12 Week group) due to an AE.

Table 26 presents key demographic and baseline disease characteristics. The majority of patients (63%) had genotype 3 HCV infection; 34% of patients had genotype 2 HCV infection. Demographic and baseline disease characteristics were generally balanced across both treatment groups.

Table 26. FUSION: Key Demographic and Disease Baseline Characteristics

	FUSION	
	SOF+RBV 12 Weeks	**SOF+RBV 16 Weeks**
	N = 103	**N = 98**
Mean age (range), years	54 (30, 69)	54 (24, 70)
Male, n (%)	73 (71%)	67 (68%)
White, n (%)	88 (85%)	86 (88%)
Mean BMI (range), kg/m^2	28 (19, 43)	29 (20, 44)
IL28B CC allele, n (%)	31 (30%)	30 (31%)
Genotype 3, n (%)	64 (62%)	63 (64%)
Mean Baseline HCV RNA (range), log_{10} IU/mL	6.5 (4.7, 7.6)	6.5 (5.1, 7.6)
Cirrhosis, n (%)	36 (35%)	32 (33%)
Prior Relapse, n (%)	78 (76%)	73 (74%)

BMI = body mass index; HCV = hepatitis C virus; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir

Table 27 summarizes SVR12 overall and by HCV genotype and other key subgroups in the FUSION study. The forest plot and CIs for the subgroup analyses are provided in Appendix 2. The primary efficacy endpoint of superiority was met in patients with genotype 2 or 3 HCV infection with 12 and 16 weeks of SOF+RBV treatment compared with an historic control SVR12 rate of 25%, with 50% and 73% of patients achieving SVR12, respectively ($p < 0.001$ for both). Treatment with 16 weeks of SOF+RBV resulted in higher SVR12 rates compared with the shorter treatment duration of 12 weeks. The difference in the percentage of patients who achieved SVR12 between the two treatment groups (SOF+RBV 12 Week group – SOF+RBV 16 Week group) was statistically significant ($p < 0.001$; –23% [95% CI: –35% to –11%] in favor of the SOF+RBV 16 Week group. For the SOF+RBV 12 Week group, 50% (50 of 100 patients) did not achieve SVR12: 47% (47 of 100 patients with HCV RNA < LLOQ at end of treatment) relapsed and 3% (3 of 100 patients) did not

have SVR12 for reasons other than virologic failure. For the SOF+RBV 16 Week group, 26 of 95 patients (27%) did not achieve SVR12, with all patients relapsing.

Subgroup analyses indicated that the differences in SVR12 rates between 12 and 16 weeks of SOF+RBV treatment were consistent with those observed in the overall population and favored the SOF+RBV 16 Week group over the SOF+RBV 12 Week group. Subgroup analyses showed generally similar SVR12 rates for age, race, ethnicity, baseline BMI, IL28B genotype, and baseline HCV RNA. For both treatment groups, a multivariate logistic regression analysis showed that HCV genotype 2 was significantly associated with a higher SVR rate ($p < 0.001$ and $p = 0.003$ for the SOF+RBV 12 Week and 16 Week groups, respectively). Drug exposure (GS-331007 AUC_{tau}) was determined to have a statistically significant relationship on SVR12 rates in patients in the SOF+RBV 16 Week group with genotype 3 HCV infection. There was no evidence for an exposure efficacy relationship in patients with genotype 2 HCV infection.

Cirrhotic patients with genotype 2 HCV infection had similar SVR12 rates in the SOF+RBV 12 Week and 16 Week groups, whereas cirrhotic patients with genotype 3 HCV infection had higher SVR12 rates in the SOF+RBV 16 Week group compared with the SOF+RBV 12 Week group. In the SOF+RBV 12 Week group, a higher SVR12 rate was observed in non-cirrhotic patients than cirrhotic patients; this difference was less pronounced in the SOF+RBV 16 Week group. In the patients with genotype 3 HCV infection with cirrhosis, there was a large difference in SVR12 rates between cirrhotic and non-cirrhotic patients following 12 weeks of SOF+RBV treatment, but this difference was attenuated when patients received 16 weeks of SOF+RBV treatment. This difference may be due to the combined impact of cirrhosis and prior treatment failure on the response rate with the 12-week treatment duration, which was partially negated by the additional 4 weeks of treatment in the SOF+RBV 16 Week group.

Table 27. FUSION: SVR12 Overall and by Key Subgroup

	FUSION					
	Genotype 2/3		Genotype 2		Genotype 3	
	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks
	N = 100 n/N (%)	N = 95 n/N (%)	N = 36 n/N (%)	N = 32 n/N (%)	N = 64 n/N (%)	N = 63 n/N (%)
Overall	50/100 (50%)[a]	69/95 (73%)[a]	31/36 (86%)	30/32 (94%)	19/64 (30%)	39/63 (62%)
95% CI	40% to 60%	63% to 81%	71% to 95%	79% to 99%	19% to 42%	49% to 74%
Cirrhosis Status						
No Cirrhosis	39/64 (61%)	48/63 (76%)	25/26 (96%)	23/23 (100%)	14/38 (37%)	25/40 (63%)
Cirrhosis	11/36 (31%)	21/32 (66%)	6/10 (60%)	7/9 (78%)	5/26 (19%)	14/23 (61%)
IL28B Genotype						
CC	15/30 (50%)	19/27 (70%)	6/7 (86%)	9/11 (82%)	9/23 (39%)	10/16 (63%)
Non-CC	35/70 (50%)	50/68 (74%)	25/29 (86%)	21/21 (100%)	10/41 (24%)	29/47 (62%)
Baseline HCV RNA						
< 6 $\log_{10}$ IU/mL	13/26 (50%)	18/29 (62%)	8/9 (89%)	3/3 (100%)	5/17 (29%)	15/26 (58%)
≥ 6 $\log_{10}$ IU/mL	37/74 (50%)	51/66 (77%)	23/27 (85%)	27/29 (93%)	14/47 (30%)	24/37 (65%)
Response to Prior HCV Treatment						
Nonresponse	11/25 (44%)	16/25 (64%)	7/10 (70%)	7/8 (88%)	4/15 (27%)	9/17 (53%)
Relapse/ Breakthrough	39/75 (52%)	53/70 (76%)	24/26 (92%)	23/24 (96%)	15/49 (31%)	30/46 (65%)

	FUSION					
	Genotype 2/3		Genotype 2		Genotype 3	
	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks
	N = 100 n/N (%)	N = 95 n/N (%)	N = 36 n/N (%)	N = 32 n/N (%)	N = 64 n/N (%)	N = 63 n/N (%)
Age at Baseline						
< 50 years	9/21 (43%)	16/23 (70%)	5/6 (83%)	3/4 (75%)	4/15 (27%)	13/19 (68%)
≥ 50 years	41/79 (52%)	53/72 (74%)	26/30 (87%)	27/28 (96%)	15/49 (31%)	26/44 (59%)
Sex						
Male	30/71 (42%)	42/64 (66%)	18/23 (78%)	20/22 (91%)	12/48 (25%)	22/42 (52%)
Female	20/29 (69%)	27/31 (87%)	13/13 (100%)	10/10 (100.0%)	7/16 (44%)	17/21 (81%)
Race						
Black	5/5 (100%)	1/1 (100%)	4/4 (100%)	0/0	1/1 (100%)	1/1 (100%)
Non Black	45/95 (47%)	68/94 (72%)	27/32 (84%)	30/32 (94%)	18/63 (29%)	38/62 (61%)
Ethnicity						
Hispanic or Latino	4/10 (40%)	5/8 (63%)	4/5 (80%)	1/1 (100%)	0/5	4/7 (57%)
Not Hispanic or Latino	46/90 (51%)	63/86 (73%)	27/31 (87%)	29/31 (94%)	19/59 (32%)	34/55 (62%)
Baseline BMI						
< 30 kg/m^2	39/71 (55%)	43/61 (70%)	23/25 (92%)	15/16 (94%)	16/46 (35%)	28/45 (62%)
≥ 30 kg/m^2	11/29 (38%)	26/34 (76%)	8/11 (73%)	15/16 (94%)	3/18 (17%)	11/18 (61%)

BMI = body mass index; CI = confidence interval; HCV = hepatitis C virus; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR12= sustained virologic response 12 weeks after cessation of study drug

Note: Three patients each in the SOF+RBV 12 Week and 16 Week groups were determined to have genotype 2 HCV infection at screening, but were shown to have recombinant genotype 1/2 HCV infection upon further sequencing and were excluded from this analysis.

Note: The exact 95% CI for the proportion within treatment group is based on the Clopper-Pearson method.

a The primary efficacy endpoint of superiority was met in patients with genotype 2 or 3 HCV infection with 12 and 16 weeks of SOF+RBV treatment compared with an historic control SVR12 rate of 25%, with 50% and 73% of patients achieving SVR12, respectively ($p < 0.001$ for both).

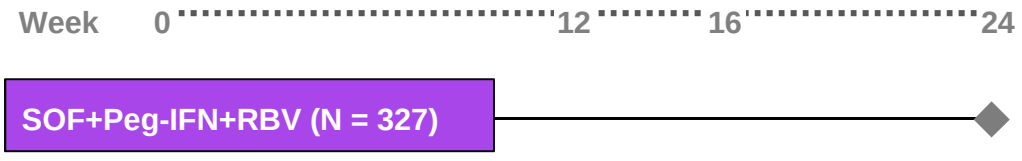
6.2.6. Efficacy of SOF+Peg-IFN+RBV Treatment in Patients With Chronic Genotype 1, 4, 5, and 6 HCV Infection

6.2.6.1. NEUTRINO: Treatment-Naive Patients with Chronic Genotype 1, 4, 5, or 6 HCV Infection

NEUTRINO was a Phase 3, multicenter, open-label, single-group study evaluating the efficacy, safety, and tolerability of SOF+Peg-IFN+RBV in treatment-naive patients with chronic genotype 1, 4, 5, or 6 HCV infection. A single-group study design was selected to allow inclusion of patients with genotype 4, 5, or 6 HCV infection. A blinded study was not possible due to the complex response guided treatment algorithms for the current protease inhibitor-based regimens for genotype 1 HCV infection with treatment durations of 24 to 48 weeks for genotype 1 HCV infection.

Figure 8 presents the study design for the NEUTRINO study. Eligible patients received SOF+Peg-IFN+RBV for 12 weeks. Of the 327 who received at least one dose of study drug, 54 patients (17%) had evidence of cirrhosis at screening.

Figure 8. NEUTRINO: Schema of Study Design



Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug

The primary efficacy analysis assessed whether patients who received SOF+Peg-IFN+RBV for 12 weeks achieved an SVR12 rate > 60%. The 60% SVR null rate was derived from Phase 3 telaprevir (ADVANCE study) and boceprevir (SPRINT2 study) data and accounted for the higher number of cirrhotic patients in the NEUTRINO study, the improved safety profile, and shorter treatment duration {17996}, {17492}, {25285}, {24932}. The 95% CI on the SVR12 rates was constructed based on exact method. Superiority was established if the 2-sided 1-sample exact test p-value was < 0.05.

A total of 327 patients were enrolled and received at least one dose of study drug. Of these 327 patients, only 7 patients (2%) discontinued study treatment. The reasons for discontinuation were AE (2%, 5 patients), protocol violation (< 1%, 1 patient), and withdrawal by patient (< 1%, 1 patient).

Table 28 presents key demographic and baseline disease characteristics. The majority of patients had genotype 1a HCV infection (69%); 66 patients (20%) had genotype 1b, one patient (< 1%) had genotype 1a/1b, 28 patients (9%) had genotype 4, one patient (< 1%) had genotype 5, and six patients (2%) had genotype 6 HCV infection.

Table 28. NEUTRINO: Key Demographic and Disease Baseline Characteristics

	NEUTRINO
	SOF+Peg-IFN+RBV 12 Weeks
	N = 327
Mean age (range), years	52 (19, 70)
Male, n (%)	209 (64%)
Black, n (%)	54 (17%)
Hispanic, n (%)	46 (14%)
Mean BMI (range), kg/m^2	29 (18, 56)
IL28B CC allele, n (%)	95 (29%)
Genotype 1, n (%)	292 (89%)
Genotype 4, 5, or 6, n (%)	35 (11%)
Mean Baseline HCV RNA (range), log_{10} IU/mL	6.4 (2.1, 7.6)
Cirrhosis, n (%)	54 (17%)

BMI = body mass index; HCV = hepatitis C virus; Peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir

Table 29 presents the SVR12 rate for the NEUTRINO study. The result of the Phase 2 ATOMIC study evaluating the same treatment regimen is shown for comparison. The primary efficacy endpoint of superiority was met for SOF+Peg-IFN+RBV treatment for 12 weeks in the NEUTRINO study compared with a predefined historic control SVR rate of 60%, with 90% of patients with genotype 1, 4, 5, or 6 HCV infection achieving SVR12 after completing therapy ($p < 0.001$). Although the NEUTRINO study included more patients with cirrhosis, the SVR results replicated those observed in the ATOMIC study. In the NEUTRINO study, 32 of 327 patients (10%) did not achieve SVR: 9% (28 of 326 patients with HCV RNA < LLOQ at end of treatment) relapsed and 1% (4 of 327 patients) did not have SVR12 for reasons other than virologic failure (eg, lost to follow-up or withdrew consent).

Table 29. NEUTRINO and ATOMIC: SVR Rates

	Phase 3 NEUTRINO	Phase 2 ATOMIC
	SOF+Peg-IFN+RBV 12 Weeks	
	N = 327 n/N (%)	N = 52 n/N (%)
SVR[a]	295/327 (90%)[b]	47/52 (90%)
95% CI	86% to 93%	79% to 97%
Genotype		
1 (1a, 1b, 1a/1b)	261/292 (89%)	47/52 (90%)
4	27/28 (96%)	0
5	1/1 (100%)	0
6	6/6 (100%)	0

CI = confidence interval; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR= sustained virologic response; SVRxx = sustained virologic response xx weeks after cessation of study drug

a In the ATOMIC study, SVR24 is presented. In the NEUTRINO study, SVR12 is presented.

b Compared with a predefined historic control SVR rate of 60%, with 90% of patients with genotype 1, 4, 5, or 6 HCV infection achieving SVR12 after completing therapy (95% CI: 86% to 93%, $p < 0.001$).

Table 30 presents SVR12 analyses by key subgroups. The forest plot and CIs for the subgroup analyses are provided in Appendix 3. Subgroup analyses demonstrated that all subgroups had high SVR rates (≥ 80%). Rates of SVR12 did not differ greatly by HCV genotype: 92% for patients with genotype 1a, 82% for patients with genotype 1b, and 97% for patients with genotype 4, 5, or 6. Although patients with genotype 1a HCV infection had a numerically higher response than patients with genotype 1b HCV infection, patients with genotype 1b HCV infection had slightly higher rates of several baseline characteristics typically associated with lower treatment response rates (eg, IL28B non-CC allele, black race, higher mean age).

As expected with an interferon-based regimen, patients with the IL28B CC allele had a higher SVR12 rate than patients with non-CC (CT or TT) IL28B alleles. Non-cirrhotic patients also appeared to have higher SVR12 rates than cirrhotic patients. Of note, there was little difference in SVR12 rates between black and non-black patients. A multivariate logistic regression analysis showed cirrhosis ($p = 0.002$) and the IL28B non-CC genotypes ($p = 0.006$) were strongly associated with lower SVR rates. No statistically significant relationship was observed between SVR12 rates and exposure (GS-331007 AUC_{tau}) based on multivariate logistic regression analysis, indicating PK, in the context of clinical, demographic, and baseline characteristics, was not a predictor of response.

Table 30. NEUTRINO: SVR12 Overall and by Key Subgroups

	NEUTRINO
	SOF+Peg-IFN+RBV (N = 327)
	n/N (%)
Overall	**295/327 (90%)[a]**
95% CI	86% to 93%
Genotype	
1 (1a, 1b, 1a/1b)	261/292 (89%)
1a	206/225 (92%)
1b	54/66 (82%)
4, 5, or 6	34/35 (97%)
Cirrhosis Status	
No Cirrhosis	252/273 (92%)
Cirrhosis	43/54 (80%)
IL28B Genotype	
CC	93/95 (98%)
Non-CC	202/232 (87%)
Baseline HCV RNA	
< 6 $\log_{10}$ IU/mL	68/71 (96%)
≥ 6 $\log_{10}$ IU/mL	227/256 (89%)
Age at Baseline	
< 50 years	104/110 (95%)
≥ 50 years	191/217 (88%)
Sex	
Male	184/209 (88%)
Female	111/118 (94%)
Race	
Black	47/54 (87%)
Non-Black	248/273 (91%)
Ethnicity	
Hispanic or Latino	42/46 (91%)
Not Hispanic or Latino	253/281 (90%)
Baseline BMI	
< 30 kg/m^2	184/198 (93%)
≥ 30 kg/m^2	111/129 (86%)

BMI = body mass index; CI = confidence interval; HCV = hepatitis C virus; Peg-IFN = pegylated interferon; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR12 = sustained virologic response 12 weeks after cessation of study drug

a Compared with a predefined historic control SVR rate of 60%, with 90% of patients with genotype 1, 4, 5, or 6 HCV infection achieving SVR12 after completing therapy (95% CI: 86% to 93%, $p < 0.001$).

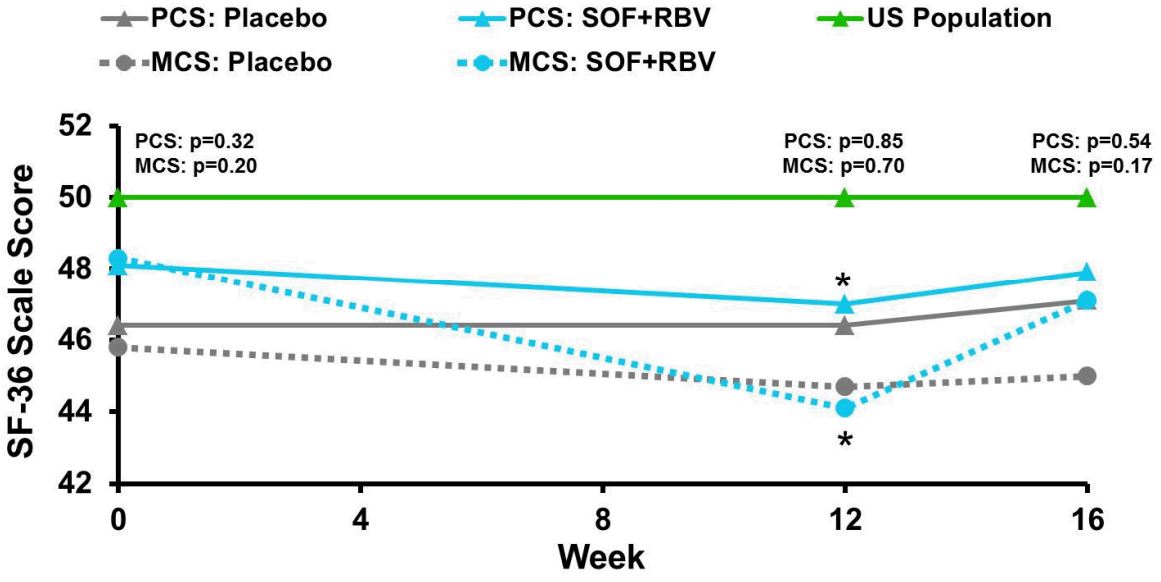
6.2.7. Patient Reported Outcomes for Phase 3 Registration Studies

The impact of treatment with SOF-containing regimens on patients' HRQL was assessed in the Phase 3 registration studies. The SF-36 self-administered questionnaire for patient-reported outcomes (PROs) was administered before, during, and after treatment. This questionnaire assesses HRQL for the following parameters: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The questionnaire also includes two summary scores, physical component summary (PCS) score and mental component summary (MCS) score, which summarize the physical and mental health components, respectively. The minimal clinically important difference for this questionnaire is considered to be two points for the two summary scores {25930}. In addition, the FACIT-F (PRO: fatigue) and WPAI (work productivity and activity) were administered in the FUSION and NEUTRINO studies.

6.2.7.1. Results of SF-36

Figure 9 shows the HRQL scores in the POSITRON study. No difference in HRQL was observed between the SOF+RBV and placebo groups at any of the time points during the study. However, at the end of treatment, when each treatment group was compared with the respective baseline level, decrements were observed in SF-36 scores of those patients receiving SOF+RBV treatment (decrements of 1.54 for PCS [p = 0.0145] and 5.58 for MCS [p < 0.0001]). Similar decrements were not observed for the placebo group. Importantly, at four weeks after the end of treatment, no significant reductions in HRQL remained and no difference was observed between the two treatment groups (p > 0.1).

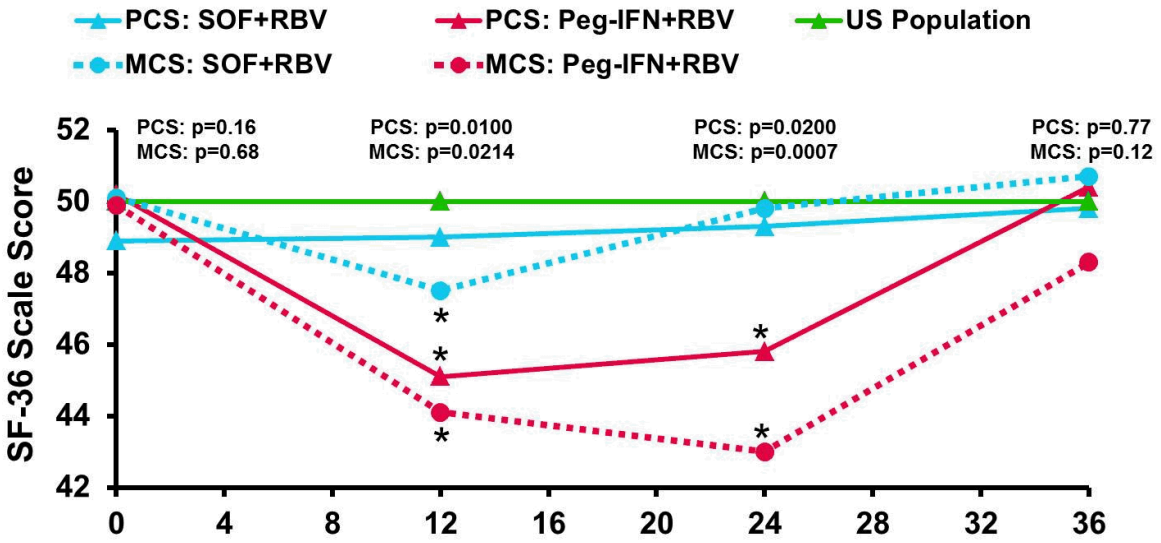
Figure 9. POSITRON: Health-Related Quality of Life by SF-36



MCS = mental component summary; PCS = physical component summary; RBV = ribavirin; SOF = sofosbuvir
Note: p-value of the difference between the treatment groups; * p < 0.05 from baseline.

Figure 10 shows the HRQL scores in the FISSION study. The baseline HRQL scores were similar between the two treatment groups. However, at the end of treatment, both the PCS and MCS were significantly higher in patients who had received SOF+RBV compared with those patients who had received Peg-IFN+RBV. The decrements in HRQL were significant for both the PCS and MCS in the Peg-IFN+RBV group (an average decrease of 4.03 and 7.37, respectively; $p < 0.05$ for both scores). For the SOF+RBV group, only the MCS significantly decreased (a decrement of 3.41; $p < 0.05$). However, this decrease in MCS was significantly less than the Peg-IFN+RBV group ($p = 0.0123$).

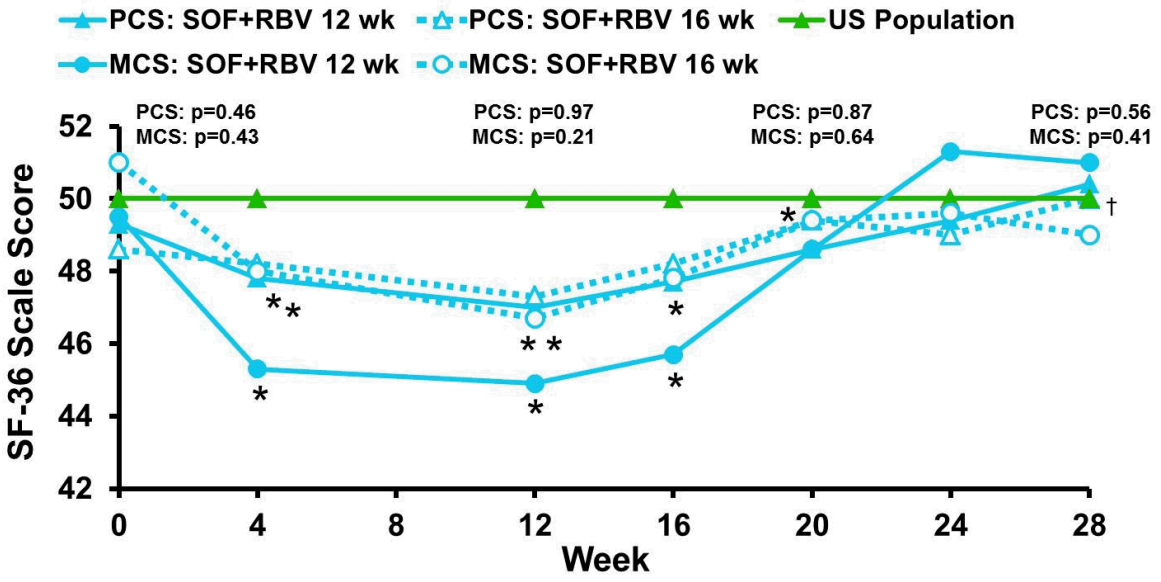
Figure 10. FISSION: Health-Related Quality of Life by SF-36



MCS = mental component summary; PCS = physical component summary; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir
Note: p-value of the difference between the treatment groups; * $p < 0.05$ from baseline.

Figure 11 shows the HRQL scores in the FUSION study. The SF-36 scores were not different between treatment groups at any time point. Significant decrements in the MCS were observed over the entire course of treatment in both treatment groups (range, 3.30 and 4.49; $p < 0.01$ for both treatment groups), but these decrements resolved after the end of treatment in both treatment groups ($p > 0.05$ for both treatment groups). These data suggests that the additional 4 weeks of active treatment did not result in any additional decrement in PRO measures. At 12 weeks after the end of treatment, most of the HRQL scores show significant improvement as compared with the baseline scores in the patients with SVR (patients who did not achieve SVR were not follow after 4 weeks post-treatment).

Figure 11. FUSION: Health-Related Quality of Life by SF-36

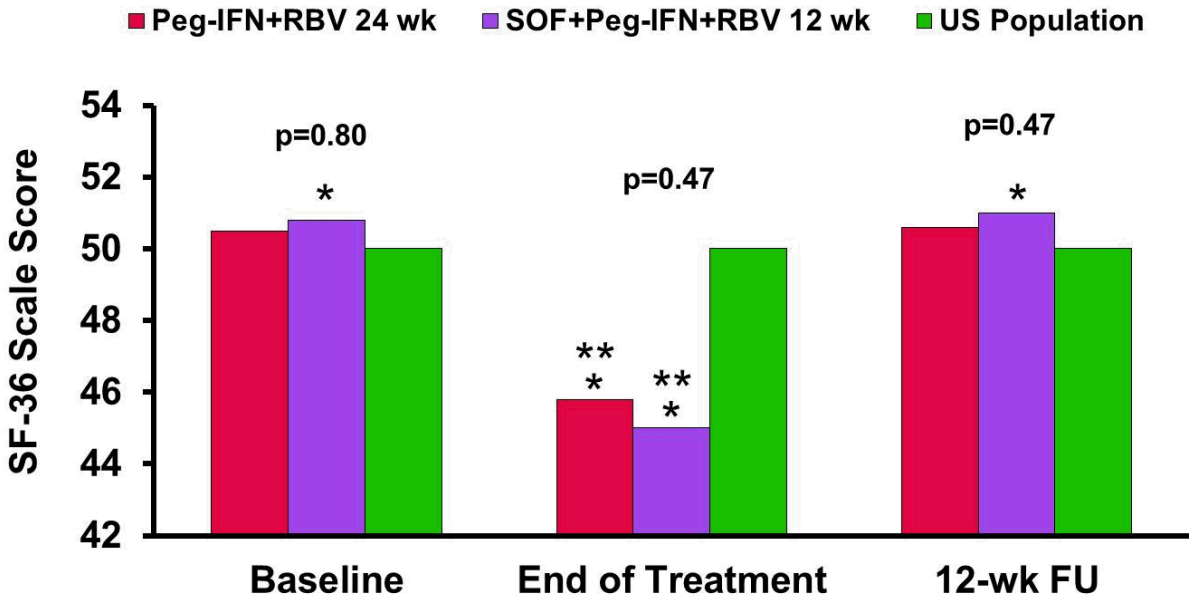


MCS = mental component summary; PCS = physical component summary; RBV = ribavirin; SOF = sofosbuvir
Note: p-value of the difference between the treatment groups; * p < 0.05 from baseline.

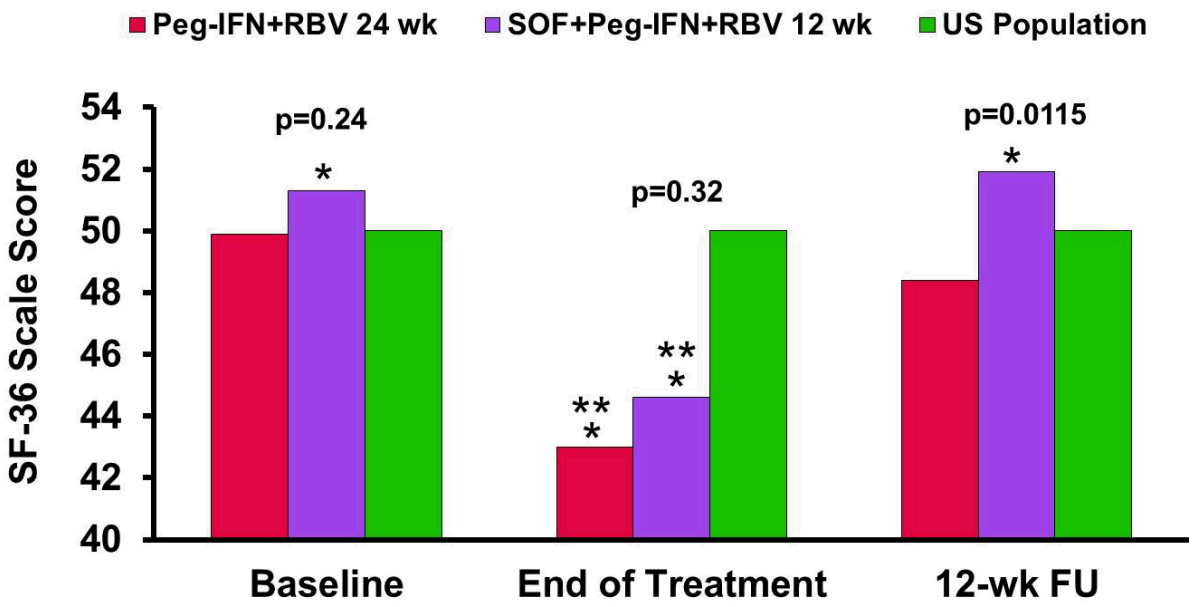
Figure 12 shows the HRQL scores in the NEUTRINO study. Patients had major decrements in HRQL in nearly all SF-36 scales. Four weeks after the end of treatment, the magnitudes of all decrements in SF-36 decreased; by 12 week after the end of treatment, all SF-36 scales had returned to their baseline levels.

Figure 12. FISSION and NEUTRINO: Health-Related Quality of Life by SF-36

PCS Score



MCS Score



FU = follow-up; MCS = mental component summary; PCS = physical component summary ; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir
Note: Numerical p-values are for the difference between treatment groups; * $p < 0.05$ when compared with population mean; and ** $p<0.05$ when compared with patients' baseline.

6.2.7.2. Predictors of HRQL, PROs, and WPAI

In all four studies, baseline depression and fatigue were the major independent predictors of lower PROs or higher work and activity impairment before, during, and after treatment. For a number of PROs, more impairment was also associated with the history of pre-treatment anxiety (regardless of time point) and the presence of liver cirrhosis (for CLDQ-HCV and work impairment after the end of treatment only). Also, in some studies, older age and higher BMI were associated with lower PCS and higher MCS at different time points, while female gender was associated with lower both PCS and MCS at different time points. During treatment, treatment-related anemia was a predictor of lower PCS at the end of treatment in POSITRON and FUSION study and lower MCS in the FISSION study. Additionally, patients receiving Peg-IFN, fatigue and depression were independent predictors of impairments in PRO measures.

6.2.7.3. Conclusions

Treatment with SOF+RBV had little effect on patients' HRQL. There was also minimal effect with SOF+RBV treatment compared with placebo in the POSITRON study and substantially less impact compared with Peg-IFN+RBV treatment in the FISSON study. Extending the duration of SOF+RBV treatment from 12 to 16 weeks did not negatively affect HRQL. In contrast, when Peg-IFN was added to SOF+RBV in the NEUTRINO study, there was a significant negative impact on HRQL; this result was not surprising, as this negative impact has been previously reported for Peg-IFN+RBV treatment.

6.2.8. Efficacy of SOF+RBV Treatment in Patients With Chronic HCV Infection Awaiting Liver Transplantation

Chronic HCV infection is the primary cause of cirrhosis and liver failure leading to orthotopic liver transplantation in North America and accounts for approximately 40% to 50% of all liver transplantations {23299}, {13693}. There is no standard-of-care treatment available for chronic HCV-infected patients awaiting liver transplantation or for those who have received liver transplantation and have had a recurrence of their HCV infection. Current interferon-based therapies for HCV are relatively ineffective, poorly tolerated, and not approved for patients with decompensated liver disease or those who are also transplantation candidates.

Infection of the uninfected, transplanted liver is universal and is associated with accelerated morbidity and mortality {19796}. The rate of accelerated, progressive liver disease and cirrhosis in the setting of immunosuppression in the posttransplantation period is high, with rates of moderate chronic hepatitis as high as 27% after a median of 3 years and the progression to cirrhosis in 8% of patients after a median of approximately 4 years {23819}. Complications of re-infection in patients receiving necessary post-transplantation immunosuppressive medications are common and can be both serious and severe due to the accelerated nature of recurrent HCV infection. Although current therapies for HCV are sometimes used after liver transplantation (preemptively or after recurrent histological disease is established), management of recurring HCV infection with current therapies in the

post-transplantation setting is complex because most posttransplantation patients do not tolerate the side effects of interferon-based therapies as well {19796}.

The Pre-Transplant study focused on patients with hepatocellular carcinoma awaiting liver transplantation because their time to liver transplantation is generally less than one year, considerably shorter than patients with end-stage liver disease awaiting transplantation. This shorter duration allowed for a more rapid proof-of-principle of efficacy of SOF+RBV treatment for the prevention of post-transplantation recurrence of HCV infection.

The Pre-Transplant study is an ongoing Phase 2, open-label study evaluating the efficacy of SOF+RBV administered prior to liver transplantation to prevent HCV infection recurrence following liver transplantation in 61 patients with genotypes 1 through 6 HCV infection and hepatocellular carcinoma meeting the Milan criteria who were within 1 year of an anticipated liver transplantation. Patients were enrolled to receive SOF 400 mg once daily and RBV 1000 or 1200 mg daily (divided dose) for a maximum of 24 weeks or until time of transplantation, whichever came first. The primary efficacy endpoint was proportion of patients with pTVR (defined as HCV RNA < LLOQ at Week 12 after transplantation).

The majority of the 61 patients had genotype 1 HCV infection (74%) while 13%, 11%, and 2% of the patients had genotypes 2, 3, and 4 HCV infection, respectively. The majority of patients had an IL28B non-CC allele (78%). The baseline CPT scores ranged from 5 to 8, with scores of 5, 6, 7, and 8 in 43%, 30%, 23%, and 5% of the patients, respectively. The majority of patients (72%) were classified as CPT A; the remaining 28% of patients were classified as CPT B. The baseline model for end-stage liver disease (MELD) score ranged from 6 to 14, with approximately half of patients (49%) with a score of 7 or 8. The majority of patients (75%) received prior HCV treatment.

Of the 61 patients who received at least one dose of SOF+RBV, 41 patients underwent a liver transplantation. Overall, 38 of these 41 patients (93%) had HCV RNA < LLOQ at the time of liver transplantation. One patient was transplanted with an HCV-infected liver and is not part of the posttransplantation analysis.

Table 31 presents the posttransplantation virologic response by visit for the 37 patients who had received any duration of SOF+RBV treatment and had HCV RNA < LLOQ at the last measurement before transplantation.

Table 31. Pre-Transplant Study: Posttransplantation Virologic Response by Visit

	SOF+RBV (N = 37)
Posttransplant Week 1	
< LLOQ	31/37 (84%)
90% CI	70% to 93%
Posttransplant Week 2	
< LLOQ	29/37 (78%)
90% CI	64% to 89%
Posttransplant Week 4	
< LLOQ	26/36 (72%)
90% CI	57% to 84%
Posttransplant Week 8	
< LLOQ	26/36 (72%)
90% CI	57% to 84%
Posttransplant Week 12	
< LLOQ	23/35 (66%)
90% CI	50% to 79%
Posttransplant Week 24	
< LLOQ	17/24 (71%)
90% CI	52% to 85%

CI = confidence interval; HCV = hepatitis C virus; LLOQ = lower limit of quantitation; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir

Note: The 90% CI for the proportion of patients with HCV RNA < LLOQ was based on the Clopper-Pearson method.

Note: Patients with last HCV RNA prior to transplantation ≥ LLOQ or transplanted with an HCV-infected liver were excluded from the pTVR endpoints.

In this study to 28 June 2013, 35 of 37 patients have been followed to post-transplantation Week 12, and 23 of these patients (66%) have achieved a pTVR. For the patients who were classified as CPT A and B, 15 of 26 patients (58%) and 8 of 9 patients (89%) had HCV RNA < LLOQ at post-transplantation Week 12, respectively. Of the 24 patients who have reached post-transplantation Week 24, 17 patients (71%) had HCV RNA < LLOQ. There were no identifiable differences in the nine patients with observed recurrent HCV infection, with the exception of genotype. Of the nine patients with observed recurrence, six (of 13 total) had genotype 1b, two (of 14 total) had genotype 1a, and one (of 9 with genotype 2 or 3 [total]) had genotype 3a HCV infection. No S282T mutations were observed in any patient post-transplantation with recurrent HCV infection. Importantly, the prevention of reinfection of the liver graft appears to be independent of the duration of SOF+RBV treatment received prior to transplantation, provided patients have HCV RNA < LLOQ at the time of transplantation.

A total of 11 of 15 patients who completed 24 weeks of SOF+RBV treatment and discontinued treatment prior to transplantation with an observed or imputed Week 4 post-treatment follow-up HCV RNA value relapsed during post-treatment follow-up. The protocol was therefore amended (Amendment 4) to extend the treatment duration from 24 to 48 weeks or the time of transplantation. The rate of relapse after 24 weeks of treatment in this patient population and the need for HCV RNA to be < LLOQ at the time of transplantation suggests that patients should continue on SOF+RBV treatment until the time of transplantation.

6.2.9. Efficacy of Sofosbuvir in Collaborative Studies

6.2.9.1. NIAID Study 11-I-0258 in Patients with Genotype 1 HCV Infection (SPARE)

NIAID is sponsoring an ongoing Phase 1/2a, open-label study evaluating the efficacy of SOF and weight-based dose or low-dose RBV for 24 weeks in treatment-naive patients with genotype 1 HCV infection who had a high proportion of traditionally negative predictors for treatment outcome. The study was enrolled in 2 parts. In Part 1, nine patients with early to moderate stage fibrosis (F0-F2) and one patient with advanced stage fibrosis were enrolled and received SOF 400 mg orally once daily and weight-based RBV 1000 or 1200 mg orally daily (divided dose) for 24 weeks. In Part 2, a total of 50 patients with all stages of fibrosis (F0-F4) were randomized to receive SOF 400 mg orally once daily and either weight-based RBV (1000 or 1200 mg orally daily [divided dose]) or low-dose RBV (600 mg orally once daily) for 24 weeks.

Table 32 presents demographic and general baseline characteristics.

Table 32. 11-I-0258: Demographics and Baseline Characteristics

Characteristic	Part 1	Part 2	
	SOF+ Weight-Based RBV (N = 10)	**SOF+ Weight-Based RBV (N = 25)**	**SOF+ Low-Dose RBV (N = 25)**
Median Age (IQR), years	54 (50, 57)	54 (51, 56)	55 (48, 59)
Male, n (%)	4 (40%)	19 (76%)	14 (56%)
Black, n (%)	9 (90%)	18 (72%)	23 (92%)
Median BMI (IQR), kg/m^2	26 (26, 34)	28 (25, 31)	30 (27, 37)
IL28B CC allele, n (%)	3 (33%)	4 (16%)	4 (16%)
Genotype 1a, n (%)1a	6 (60%)	20 (80%)	16 (64%)
Median Baseline HCV RNA (IQR), log_{10} IU/mL	6.8 (6, 7.1)	6.2 (5.4, 6.4)	6.1 (5.5, 6.3)
HAI Fibrosis 3–4, n (%)	1 (10%)	6 (24%)	7 (28%)

BMI = body mass index; HAI = Hepatic Activity Index ; HCV = hepatitis C virus; IQR = interquartile range; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir

Note: Weight-based RBV dose was 1000 mg daily (divided dose) for patients who weighed < 75 kg and 1200 mg/day (divided dose) for patients who weighed ≥ 75 kg. Low-dose RBV dose was 600 mg once daily.

Note: This analysis was conducted for intention-to-treat analysis set (defined as all patients who received at least one dose of study drug)

Table 33 presents the proportion of patients with SVR12 (defined as HCV RNA less than the limit of detection 12 weeks after the cessation of study drug).

Table 33. 11-I-0258: SVR12 for Patients

	Part 1	Part 2	
Treatment Week	**SOF+ Weight-Based RBV 24 Weeks (N = 10)**	**SOF+ Weight-Based RBV 24 Weeks (N = 25)**	**SOF+ Low-Dose RBV 24 Weeks (N = 25)**
SVR	9/10 (90%)	17/25 (68%)	12/25 (48%)
Overall Virologic Failure	0/10	7/25 (28%)	10/25 (40%)
Relapse	0	7/24 (29%)	10/22 (45%)
Other[a]	1/10 (10%)	1/25 (4%)	3/25 (12%)

RBV = ribavirin; SOF = sofosbuvir; SVR= sustained virologic response

Note: Weight-based RBV dose was 1000 mg daily (divided dose) for patients who weighed < 75 kg and 1200 mg/day (divided dose) for patients who weighed ≥ 75 kg. Low-dose RBV dose was 600 mg once daily.

Note: This analysis was conducted for intention-to-treat analysis set (defined as all patients who received at least one dose of study drug)

a Other = Patients who did not achieve SVR12 and did not meet virologic failure criteria.

6.2.9.2. Janssen Study HPC2002 in Patients with Genotype 1 HCV Infection

Janssen is sponsoring an ongoing Phase 2, multicenter, randomized, open-label study evaluating the efficacy and safety of SOF and the nonstructural protein 3/4A (NS3/4A) protease inhibitor SMV with or without RBV for 12 or 24 weeks in non-cirrhotic patients with genotype 1 HCV infection who had a null response with prior PEG+RBV treatment (Cohort 1) or were treatment naive (Cohort 2) {23866}. Patients received SOF 400 mg once daily and SMV 150 mg once daily with or without RBV 1000 or 1200 mg daily (divided dose). For the NDA submission, only preliminary data from a subset of Cohort 1 are included and presented.

Table 34 presents SVR8. The SVR rates for patients with genotype 1a and 1b HCV infection were similar. There was no on-treatment virologic failure. Two patients relapsed: 1 patient each in the SOF+SMV+RBV 12 Week and SOF+SMV 12 Week groups. Both patients relapsed by 4 weeks after study treatment completion. Resistance to SMV was identified in 1 patient; however, no resistance to SOF was identified.

Table 34. HPC2002: SVR8 for Patients with Genotype 1 HCV Infection

Treatment	N	SVR8 n/N (%)
SOF+SMV+RBV 12 Weeks	27	26/27 (96%)
SOF+SMV 12 Weeks	14	13/14 (93%)
SOF+SMV+RBV 24 Weeks	24	4/6 (67%)
SOF+SMV 24 Weeks	15	5/5 (100%)

RBV = ribavirin; SMV = simeprevir; SOF = sofosbuvir; SVR8= sustained virologic response 8 weeks after cessation of study drug

6.2.9.3. BMS Study AI444040 in Patients with Genotype 1, 2, or 3 HCV Infection

Bristol-Myers Squibb is sponsoring and conducting a Phase 2a, randomized, open-label, 2-stage, parallel-group study evaluating the safety and efficacy of SOF 400 mg once daily in combination with the NS5A inhibitor DCV 60 mg once daily with or without RBV (1000 or 1200 mg daily [divided dose] for patients with genotype 1 HCV infection or 800 mg BID for patients with genotype 2 or 3 HCV infection) for 12 or 24 weeks in non-cirrhotic, treatment-naive patients with genotype 1, 2 or 3 HCV infection {23141}.

Table 35 presents SVR for patients with genotype 1, 2, or 3 HCV infection.

Table 35. AI444040: SVR Rates for Patients with Genotype 1, 2, or 3 HCV Infection

Treatment	Genotype	n	SVR[a] %
SOF+DCV 24 Weeks with SOF Lead-in (Group B)	2, 3	16	88%
SOF+DCV 24 Weeks (Group D)	2, 3	14	100%
SOF+DCV +RBV (Group F)	2, 3	14	93%
SOF+DCV 24 Weeks with SOF Lead-in (Group A)	1	15	93%[b]
SOF+DCV 24 Weeks (Group C)	1	14	100%
SOF+DCV +RBV 24 Weeks (Group E)	1	15	100%
SOF+DCV 12 Weeks (Group G)	1	41	98%[c,d]
SOF+DCV +RBV 12 Weeks (Group H)	1	41	95%[d,e]

DCV = daclatasvir; HCV = hepatitis C virus; LLOQ = lower limit of quantitation; RBV = ribavirin; RNA = ribonucleic acid; SOF = sofosbuvir; SVR = sustained virologic response; SVRxx = sustained virologic response xx weeks after cessation of study drug

a For Groups A, B, C, D, E, and F, SVR24 is presented. For Groups G and H, SVR4 is presented.

b One patient had detectable HCV RNA at posttreatment Week 24 had a different viral sequence pre- and post-treatment consistent with a likely reinfection; follow-up is ongoing.

c Patient was missing HCV RNA assessment at posttreatment Week 4 visit, but achieved SVR12.

d Of 68 patients who have reached their posttreatment Week 12 visit, all patients have achieved SVR12.

e One patient was missing HCV RNA assessment at posttreatment Week 4 visit, but achieved SVR12. An additional patient had HCV RNA < LLOQ at posttreatment Week 2 visit and HCV RNA of 54 IU/mL at post-treatment Week 4 visit (not confirmed), but achieved SVR12.

6.2.10. Efficacy Conclusions and Proposed Treatment Recommendation for Patients with Genotype 1, 2, 3, 4, 5, or 6 HCV Infection

6.2.10.1. Genotype 2 or 3 Infection

The current standard-of-care treatment for treatment-naive patients infected with genotype 2 or 3 HCV infection is Peg-IFN+RBV for 24 weeks {13693}. The AASLD treatment guidelines do not recommend re-treatment for patients who have failed a course of Peg-IFN+RBV; however, these patients can be re-treated with Peg-IFN+RBV for 48 weeks based on the Peg-IFN+RBV prescribing information {13693}, {24701}. Patients who are medically ineligible, intolerant, or unwilling to receive interferon treatment have no treatment option.

Table 36 summarizes SVR12 rates by genotype and cirrhosis status in the FISSION, POSITRON, and FUSION studies. In the Phase 3 SOF clinical program, patients with genotype 2 or 3 HCV infection were studied together based on the Phase 2 data in which the SVRs with SOF-containing regimens were similar. However, when SVR12 data from the Phase 3 studies and a multivariate logistic regression analysis showing that the only

consistent factor associated with response was HCV genotype are considered, it is clear that treatment responses can differ substantially between HCV genotypes 2 and 3 with SOF-containing regimens; therefore, it is appropriate to summarize the results separately.

Table 36. FISSION, POSITRON, and FUSION: SVR12 by Genotype and Cirrhosis Status

Study	Treatment	Cirrhosis Status	Genotype 2/3 n/N (%)	Genotype 2 n/N (%)	Genotype 3 n/N (%)
FISSION	SOF+RBV 12 Weeks	Overall	170/253 (67%)	68/70 (97%)	102/183 (56%)
		No Cirrhosis	147/204 (72%)	58/59 (98%)	89/145 (61%)
		Cirrhosis	23/49 (47%)	10/11 (91%)	13/38 (34%)
	Peg-IFN+RBV 24 Weeks	Overall	162/243 (67%)	52/67 (78%)	110/176 (63%)
		No Cirrhosis	143/193 (74%)	44/54 (81%)	99/139 (71%)
		Cirrhosis	19/50 (38%)	8/13 (62%)	11/37 (30%)
POSITRON[a]	SOF+RBV 12 Weeks	Overall	161/207 (78%)	101/109 (93%)	60/98 (61%)
		No Cirrhosis	142/176 (81%)	85/92 (92%)	57/84 (68%)
		Cirrhosis	19/31 (61%)	16/17 (94%)	3/14 (21%)
FUSION	SOF+RBV 12 Weeks	Overall	50/100 (50%)	31/36 (86%)	19/64 (30%)
		No Cirrhosis	39/64 (61%)	25/26 (96%)	14/38 (37%)
		Cirrhosis	11/36 (31%)	6/10 (60%)	5/26 (19%)
	SOF+RBV 16 Weeks	Overall	69/95 (73%)	30/32 (94%)	39/63 (62%)
		No Cirrhosis	48/63 (76%)	23/23 (100%)	25/40 (63%)
		Cirrhosis	21/32 (66%)	7/9 (78%)	14/23 (61%)

Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; SVR12= sustained virologic response 12 weeks after cessation of study drug

a None of the patients in the placebo group in the POSITRON study achieved SVR12 and results for the placebo group are not included in this table.

6.2.10.2. Genotype 2 HCV Infection

For patients with genotype 2 HCV infection, the overall SVR12 rates for SOF+RBV treatment for 12 weeks were high across the Phase 3 studies. The SVR12 rates ranged from 86% to 97% in treatment-experienced and treatment-naive patients, respectively, compared with an SVR12 rate of 78% in treatment-naive patients who received 24 weeks of Peg-IFN+RBV. Thus, the proposed recommended treatment for all patients with genotype 2 HCV infection is SOF+RBV for 12 weeks.

6.2.10.3. Genotype 3 HCV Infection

In contrast to the Phase 2 data, both treatment-naive and treatment-experienced patients with genotype 3 HCV infection had lower SVR rates than those patients with genotype 2 HCV infection. In addition, treatment-experienced patients had lower SVR rates than

treatment-naive patients when treated for 12 weeks; however, this difference was attenuated when treatment duration was extended to 16 weeks.

Treatment-naive patients with genotype 3 HCV infection in the FISSION and POSITRON studies who received SOF+RBV for 12 weeks had similar SVR rates (56% and 61%, respectively), which were also similar to patients who received Peg-IFN+RBV for 24 weeks 63% in the FISSION study. In contrast, treatment-experienced patients with genotype 3 HCV infection in the FUSION study who received SOF+RBV for 12 weeks had substantially lower SVR rates (30%) than treatment-naive patients treated for the same duration. However, when the treatment duration was extended from 12 to 16 weeks in the FUSION study, the SVR rate (62%) was similar to that achieved in treatment-naive patients. Since treatment-naive patient populations include a subgroup of patients that would be virologic failures if treated with Peg-IFN+RBV, it is reasonable to assume that 16 weeks of treatment will also increase the response rate in treatment-naive patients.

In order to quantify the potential improvement in SVR rates that might be observed with a 16-week regimen in treatment-naive patients with genotype 3 HCV infection, a bridging analysis using a logistic regression model was performed. A logistic regression model was fitted to combined SVR12 data from the FISSION and FUSION studies and assessed the impact of treatment duration while controlling for sex, baseline HCV RNA, and cirrhosis status.

Table 37 presents the predicted SVR12 for 16 weeks of SOF+RBV treatment in the FISSION study based on the logistic regression modeling. With an assumption of 100% of the benefit retained, the predicted SVR12 rate for treatment-naive patients following 16 weeks of SOF+RBV treatment was 78%. The sensitivity analysis show that 16 weeks of SOF+RBV treatment in treatment-naive patients could lose as much as 75% of the benefit observed in treatment-experienced patients and the predicted SVR12 rates are comparable or better than the SVR12 rate observed following Peg-IFN+RBV treatment for 24 weeks in the FISSION study. These results suggests that increasing the SOF+RBV treatment duration from 12 to 16 weeks will increase the SVR12 rate for treatment naive patients with genotype 3 HCV infection.

Table 37. FISSION: Predicted SVR12 Rates for Patients with Genotype 3 HCV Infection Based on Logistic Regression Modeling

% Benefit Retained	SOF+RBV 16 Weeks Projected SVR12 % (95% Credible Limit)
100%	78 (63, 90)
75%	74 (60, 84)
50%	68 (58, 77)
25%	62 (54, 70)

SVR12 = sustained virologic response 12 weeks after cessation of study drug

In addition, results of these bridging analyses indicate that for cirrhotic and non-cirrhotic treatment-naive patients with genotype 3 HCV infection increasing the SOF+RBV treatment duration from 12 to 16 weeks may increase the SVR12 rate to 76% and 79%, respectively.

Based on the available data in the treatment-experienced patients with genotype 3 HCV infection and the results of the bridging analysis, the proposed recommended treatment for all patients with genotype 3 HCV infection is SOF+RBV for 16 weeks.

An ongoing study is prospectively evaluating 16- and 24-week SOF+RBV treatment regimens in patients with genotype 3 HCV infection (treatment-naive and treatment-experienced patients with and without cirrhosis) (Appendix 1).

6.2.10.4. Genotype 1, 4, 5, or 6 HCV Infection

The current standard-of-care for treatment-naive patients with genotype 1 HCV infection is a protease inhibitor for varying durations in combination with Peg-IFN+RBV for a total duration of 24 or 48 weeks {19759}, {25285}, {24932}. Limitations of this treatment include poor tolerability, numerous drug-drug interactions, a high pill burden and dosing frequency, complex response-guided treatment algorithms, long-treatment duration, and a low genetic barrier to resistance that is associated with virologic breakthrough and virologic resistance in most patients who fail these regimens. The currently recommended treatment for patients with chronic genotype 4 or 6 HCV infection is Peg-IFN+RBV for 48 weeks; there is no recommended treatment for patients with chronic genotype 5 HCV infection {13693}.

In the NEUTRINO study, a statistically significant higher proportion of patients who received SOF+Peg-IFN+RBV for 12 weeks achieved SVR12 (90%) compared with a historical SVR12 rate of 60%. The NEUTRINO study confirmed the results of SOF+Peg-IFN+RBV treatment for 12 weeks in the Phase 2 ATOMIC study (SVR rates of 90% each) which are higher than those achieved with any currently available HCV treatment {25285}, {24932}.

Among the 35 patients with genotype 4, 5, or 6 HCV infection, 34 achieved SVR12 (1 patient with genotype 4 HCV infection with cirrhosis did not achieve SVR12). These results compare favorably with current standard-of-care therapy, Peg-IFN+RBV for 48 weeks, which have reported SVR results in the range of 50% to 80% for genotypes 4, 5, and 6 HCV infection {4481}, {22111}, {22602}, {22603}, {22604}, {22605}.

Of note, a high level of efficacy was demonstrated in the NEUTRINO study for all subgroups of patients (eg, genotype, cirrhosis status, IL28B genotype, baseline HCV RNA, age, sex, race, ethnicity, baseline BMI) with ≥ 80% of patients achieving SVR12 including those with cirrhosis.

The proposed recommended treatment for treatment-naive patients with genotype 1, 4, 5, or 6 HCV infection is SOF+Peg-IFN+RBV for 12 weeks.

6.2.10.5. Efficacy of SOF+RBV Treatment in Patients With Chronic HCV Infection Awaiting Liver Transplantation

The available data from studies in which SOF was administered in combination with RBV in HCV-infected patients awaiting liver transplantation suggest that SOF has a high level of efficacy in this patient population.

This study focused on patients with hepatocellular carcinoma awaiting liver transplantation because their time to liver transplantation is generally less than one year, considerably shorter than patients with end-stage liver disease awaiting transplantation. This shorter duration allowed for a more rapid proof-of-principle of efficacy of SOF+RBV for the prevention of post-transplantation recurrence of HCV infection. The patients enrolled in the Pre-Transplant study had less advanced liver disease (72% and 28% of patients were classified as CPT A and B at baseline, respectively) than the general HCV-infected patient population awaiting liver transplantation. Treatment with SOF+RBV was well tolerated in the Pre-Transplant study, with no unique safety signals identified (Section 7.4). These safety data, including data from 10 patients treated for longer than 24 weeks in this study, and the efficacy demonstrated in preventing post-transplantation recurrence of HCV infection support a broad application of these data to treat HCV-infected patients awaiting liver transplantation irrespective of the presence of hepatocellular carcinoma.

The proposed recommended treatment for HCV-infected patients awaiting liver transplantation is SOF+RBV until the time of liver transplantation.

6.2.10.6. Use With Other Direct-Acting Anti-Virals

The data from studies in which SOF was administered in combination with DAAs, DCV or SMV, suggest that SOF, when used as a backbone of therapy, may have a high level of efficacy in a number of combinations with DAAs with or without RBV across multiple HCV genotypes and patient populations.

6.3. Clinical Virology

6.3.1. Established Resistance Profiles in Vitro

In vitro resistance selection experiments in replicon cells identified S282T as the primary mutation in all genotypes (1 through 6) evaluated. Site-directed mutagenesis confirmed that the S282T mutation confers reduced susceptibility to SOF; however, the S282T mutation does not confer cross-resistance to other classes of anti-viral inhibitors and appears to increase sensitivity to RBV in vitro.

6.3.2. Baseline Resistance Data

NS5B population sequences were obtained at baseline for 1994 of 2016 patients who participated in the Phase 2 and 3 clinical studies. Of these patients, 1662 patients received a SOF-containing treatment regimen. None of the 1994 patients who were sequenced had the S282T mutation detected at baseline by population sequencing.

Baseline samples were also assessed for the baseline presence of the NS5B mutations T390I and F415Y, both previously observed in patients with virologic failure from RBV-containing regimens {21377}. A total of 39 patients who received SOF with sequence data had detectable T390I or F415Y variant at baseline as either a full mutant or a mixture. Statistical analysis demonstrated no correlation between the presence of these individual variants at baseline and treatment outcome for SOF-containing regimens.

Phylogenetic analyses of NS5B sequences from patients in all treatment groups of the 4 Phase 3 studies demonstrated that patients with genotype 2 or 3 HCV infection who were analyzed and either achieved SVR12 or failed to achieve SVR12 were genetically intermingled in their HCV sequences and showed no evidence of clustering, suggesting that intra-genotype NS5B genetic variation was not a determinant of efficacy.

6.3.3. Clinical Resistance Findings for Phase 2 and 3 Studies

Resistance analyses were attempted on plasma HCV isolates from all patients who had HCV RNA > 1000 IU/mL and an available plasma sample at the time of virologic failure or early discontinuation.

Table 38 provides a summary of the post-baseline resistance analysis population. Among patients who received SOF in the Phase 2 and 3 studies, 302 of 1662 patients qualified to be part of the resistance analysis population and, of these patients, 300 had NS5B sequences available: deep sequencing results were available from 294 patients, with > 1000 × coverage at NS5B 282 position in 272 of these patients, and population sequencing results were available from 6 patients. The S282T substitution was only detected in 1 of the 300 patients in the resistance analysis population; this patient had received SOF monotherapy and was successfully re-treated with SOF+RBV.

Table 38. Sofosbuvir Phase 2/3 Studies: Resistance Analysis Population Summary

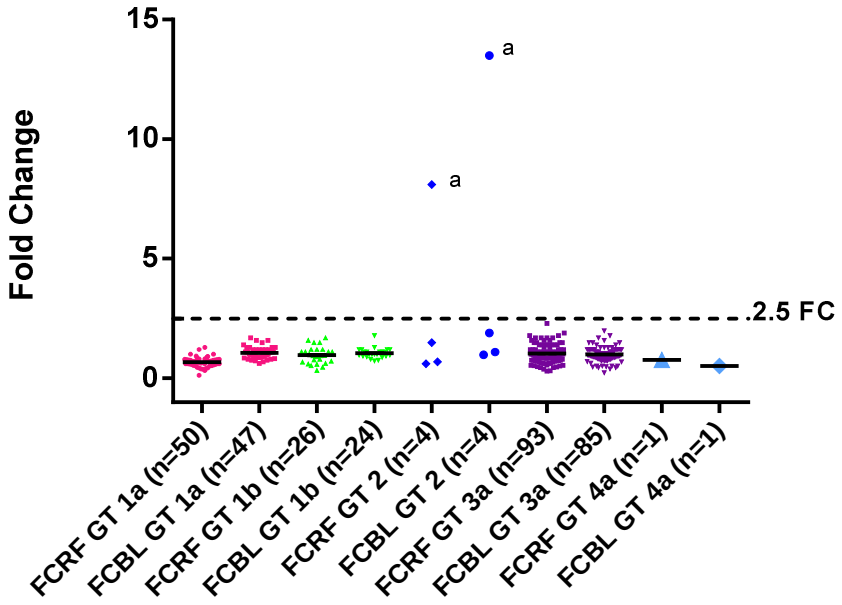
	Phase 2 Studies	Phase 3 Studies	Total
Number of Patients Receiving SOF in Resistance Analysis Population/Total Number of Patients Receiving SOF	76/671	226/991	302/1662
Number of Patients Receiving SOF in Resistance Analysis Population with Postbaseline Sequencing Data	75 (1 short NS5B) (73 deep, 2 population)	225 (17 short NS5B) (221 deep, 4 population)	300 (18 short NS5B) (294 deep, 6 population)
Number of Patients Receiving SOF in Resistance Analysis Population with the S282T Mutation Postbaseline	1	0	1
Number of Patients Receiving SOF in Resistance Analysis Population with F415Y or T390I Postbaseline	3	3	6
Number of Patients with Phenotype Data	64	110	174
Number of Patients with a Reduced Susceptibility to SOF	1	0	1

NS5B = nonstructural protein 5B; SOF = sofosbuvir

There were other NS5B substitutions observed in more than two patients. However, none of these substitutions were associated with a phenotypic change in SOF or RBV susceptibility. Phenotypic data were successfully generated from 174 patients in the resistance analysis population.

Figure 13 presents the SOF EC_{50} and EC_{90} fold change for the samples from patients with relapse compared with baseline samples or replicon references for genotype 1, 2, or 3 HCV clinical isolates from the 174 patients. With the exception of the single patient in the Phase 2 monotherapy study who developed S282T, no reduction in susceptibility to SOF or RBV was observed in HCV variants in these patients at relapse.

Figure 13. Sofosbuvir EC_{50} and EC_{90} Fold Change from Baseline and Fold Change from Reference of Genotype 1, 2, or 3 HCV Clinical Isolates from Treatment-Naive Patients



EC_{xx} = concentration of SOF inhibiting virus replication by xx%; FC = fold change; FCRF = fold change from reference; FCBL = fold change from baseline; GT = genotype; SOF = sofosbuvir

Note: Fold-change values from patients with EC_{50}/EC_{90} data from multiple time points were averaged except for the patient from the ELECTRON study who received SOF monotherapy and had S282T detectable at relapse.

a Data from the patient in the ELECTRON study who received SOF monotherapy had S282T detectable at relapse.

6.3.4. Replication Capacity of Site-directed S282T and Patient-derived Clones

The replication capacities of S282T mutants were evaluated in genotype 1 through 6 replicons. The S282T mutants replicated poorly across all HCV genotypes, with replication capacity ranging from 1% to 11% compared with corresponding wild-type replicons. In addition, a significant reduction in replication capacity (1.5% to 1.8% of wild-type) was observed in the replicon clones containing NS5B from the patient with the S282T mutation detected. These in vitro data are consistent with the short persistence of S282T in the single patient with this mutant detected following SOF monotherapy, with the lack of virologic breakthrough observed in the Phase 2 and 3 studies, and the infrequent observation of the S282T mutation in patients with relapse.

7. SAFETY

Safety data were submitted in the NDA from a total of 27 clinical studies (24 Gilead-sponsored and 3 non-Gilead-sponsored) and support the proposed SOF indication for the treatment of chronic HCV infection in combination with other agents.

The 4 Phase 3 registration studies comprise the primary safety population. The safety data from the Phase 2 studies support the safety profile observed in the primary safety population.

The 3 Phase 3 registration studies of SOF+RBV in patients with genotype 2 or 3 HCV infection assessed the safety profile of SOF+RBV treatment as compared with Peg-IFN+RBV treatment (FISSION) or placebo treatment (POSITRON); and the safety of SOF+RBV for 12 or 16 weeks of treatment was also assessed (FUSION). The fourth Phase 3 registration study, NEUTRINO, assessed the safety profile of SOF+Peg-IFN+RBV for 12 weeks in patients with genotype 1, 4, 5, or 6 HCV infection. These safety analyses included the following groups:

- 566 patients who received SOF+RBV for 12 weeks by individual study and pooled from the 12-week treatment groups in the FISSION (N = 256), POSITRON (N = 207), and FUSION (N = 103) studies
- 98 patients who received SOF+RBV for 16 weeks in the FUSION study
- 71 patients who received placebo in the POSITRON study
- 243 patients who received Peg-IFN+RBV for 24 weeks in the FISSION study
- 327 patients who received SOF+Peg-IFN+RBV for 12 weeks in the NEUTRINO study

In addition to SOF+RBV safety data for the primary safety population, safety data from 61 patients awaiting liver transplantation receiving SOF+RBV for up to 48 weeks in the Pre-Transplant study and 165 patients receiving SOF+RBV treatment for 24 weeks in the Phase 2 QUANTUM study and a Phase 2 study in Egyptian patients with genotype 4 HCV infection are presented in the following sections.

In the SOF clinical development program, patients were assessed for AEs and laboratory evaluations on a pre-specified schedule. All AEs and laboratory abnormalities discussed in this overview were treatment emergent (defined as starting from the first dose of study drug through 30 days after the last dose of any study drug). An AE was assessed by the investigator as Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), or Grade 4 and/or 5 (life-threatening and/or fatal) and as related or not related to study treatment. An AE was defined as serious if it resulted in death, hospitalization, or other medically significant events {26240}. The safety analysis set was defined as all patients who received at least one dose of study drug.

The safety data are presented for SOF+RBV treatment regimen followed by the SOF+Peg-IFN+RBV treatment regimen.

7.1. Extent of Exposure in Phase 3 Registration Studies

In the Phase 3 registration studies, the primary safety population included 991 patients with chronic HCV infection who received SOF, 71 patients who received placebo, and 243 patients who received Peg-IFN+RBV.

Table 39 presents the proportion of patients who completed their assigned treatment regimen in the Phase 3 registration studies. Overall, the SOF-containing regimens were well tolerated; 96% to 100% of patients in these groups completed treatment.

Table 39. FISSION, POSITRON, FUSION, and NEUTRINO: Proportion of Patients Who Completed Treatment

Study	Treatment Regimen	N	Completing Treatment n (%)
FISSION	SOF+RBV 12 Weeks	256	245 (96%)
	Peg-IFN+RBV 24 Weeks	243	189 (78%)
POSITRON	SOF+RBV 12 Weeks	207	201 (97%)
	Placebo 12 Weeks	71	68 (96%)
FUSION	SOF+RBV 12 Weeks	103	102 (99%)
	SOF+RBV 16 Weeks	98	98 (100%)
NEUTRINO	SOF+Peg-IFN+RBV 12 Weeks	327	320 (98%)

Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir

7.2. Safety of SOF+RBV Treatment in Patients with Chronic Genotype 2 or 3 HCV Infection in Phase 3 Registration Studies

7.2.1. Overall Summary of Adverse Events

Table 40 provides an overall summary of AEs for the FISSION, POSITRON, and FUSION studies. The placebo group had the lowest proportion of AEs (77%) and the Peg-IFN+RBV group had the highest proportion of AEs (96%) compared with the SOF+RBV groups (range, 86% to 89%). The placebo group had the lowest proportion (1%) and the Peg-IFN+RBV group had the highest proportion (19%) of Grade 3 or higher AEs compared with the SOF+RBV groups (range, 4% to 8%). The Peg-IFN+RBV group had the highest proportion of patients who had an AE that led to treatment discontinuation (11%) compared with all other groups (0% to 4%).

The incidence of Grade 3 or higher AEs, SAEs, AEs leading to discontinuation of SOF, and deaths was low for all SOF+RBV treatment groups. The safety profile was similar for SOF+RBV treatment for 12 and 16 weeks; the percentages of patients who had any AE was

similar in all groups (range, 86% to 89%). No individual Grade 3 or higher AEs occurred in more than 1% of patients receiving SOF+RBV or placebo. Grade 3 or higher AEs occurring in more than 1% of patients receiving PEG+RBV were neutropenia, fatigue, thrombocytopenia, and insomnia.

Table 40. FISSION, POSITRON, and FUSION: Overall Summary of Adverse Events

	FISSION		POSITRON		FUSION		FISSION, FUSION, POSITRON
	SOF+RBV 12 Weeks	Peg-IFN+ RBV 24 Weeks	SOF+RBV 12 Weeks	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	Pooled SOF+RBV 12 Weeks
Patients with:	N = 256 n (%)	N = 243 n (%)	N = 207 n (%)	N = 71 n (%)	N = 103 n (%)	N = 98 n (%)	N = 566 n (%)
Any AE	220 (86%)	233 (96%)	185 (89%)	55 (77%)	92 (89%)	86 (88%)	496 (88%)
Grade 3 or Higher AE	18 (7%)	45 (19%)	17 (8%)	1 (1%)	8 (8%)	4 (4%)	41 (7%)
Any SAE	7 (3%)	3 (1%)	11 (5%)	2 (3%)	5 (5%)	3 (3%)	22 (4%)
AE Leading to Treatment Discontinuation	3 (1%)	26 (11%)	4 (2%)	3 (4%)	1 (< 1%)	0	8 (1%)
Death	1 (< 1%)	0	0	0	0	0	1 (< 1%)

AE = adverse event; Peg-IFN = pegylated interferon; RBV = ribavirin; SAE = serious adverse event; SOF = sofosbuvir

7.2.2. Common Adverse Events

Table 41 presents a summary of AEs that were reported in at least 15% of patients in any treatment group. The most commonly reported AEs (ie, ≥ 15% of patients in any treatment group) generally occurred less frequently in patients receiving SOF+RBV than in patients receiving PEG+RBV. These AEs included fatigue, headache, nausea, insomnia, rash, pruritus, decreased appetite, irritability, diarrhea, myalgia, influenza-like illness, and chills; all of these AEs have been reported previously with Peg-IFN+RBV treatment {24700}, {3302}.

The most commonly reported AEs in patients in the pooled SOF+RBV 12 Week and SOF+RBV 16 Week groups were fatigue, headache, nausea, and insomnia. The three most commonly reported AEs occurring in the placebo group were similar to those reported for the two SOF+RBV treatment groups: fatigue, headache, and nausea. The frequency of commonly reported AEs was similar in patients in receiving SOF+RBV treatment for 12 and 16 weeks.

Table 41. FISSION, POSITRON, and FUSION: Adverse Events in ≥ 15% of Patients in Any Treatment Group

	FISSION		POSITRON		FUSION		FISSION, FUSION, POSITRON
	SOF+RBV 12 Weeks	Peg-IFN +RBV 24 Weeks	SOF+RBV 12 Weeks	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	Pooled SOF+RBV 12 Weeks
Preferred Term	N = 256 n (%)	N = 243 n (%)	N = 207 n (%)	N = 71 n (%)	N = 103 n (%)	N = 98 n (%)	N = 566 n (%)
Fatigue	92 (36%)	134 (55%)	91 (44%)	17 (24%)	46 (45%)	46 (47%)	229 (40%)
Headache	64 (25%)	108 (44%)	43 (21%)	14 (20%)	26 (25%)	32 (33%)	132 (23%)
Nausea	46 (18%)	70 (29%)	46 (22%)	13 (18%)	22 (21%)	20 (20%)	114 (20%)
Insomnia	31 (12%)	70 (29%)	39 (19%)	3 (4%)	21 (20%)	28 (29%)	91 (16%)
Rash	23 (9%)	43 (18%)	18 (9%)	6 (8%)	7 (7%)	12 (12%)	48 (8%)
Pruritus	19 (7%)	42 (17%)	23 (11%)	6 (8%)	12 (12%)	7 (7%)	53 (9%)
Irritability	25 (10%)	40 (16%)	19 (9%)	1 (1%)	15 (15%)	11 (11%)	58 (10%)
Decreased Appetite	17 (7%)	44 (18%)	7 (3%)	7 (10%)	9 (9%)	5 (5%)	33 (6%)
Diarrhoea	23 (9%)	42 (17%)	19 (9%)	4 (6%)	15 (15%)	6 (6%)	57 (10%)
Myalgia	21 (8%)	40 (16%)	6 (3%)	0	8 (8%)	9 (9%)	35 (6%)
Influenza-like Illness	7 (3%)	44 (18%)	8 (4%)	2 (3%)	1 (< 1%)	3 (3%)	16 (3%)
Chills	7 (3%)	43 (18%)	7 (3%)	1 (1%)	2 (2%)	0	16 (3%)

Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir

7.2.3. Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

There was one death in the Phase 3 registration studies. A patient randomized to the SOF+RBV group of the FISSION study died from cocaine and heroin intoxication on Day 1. This death was considered unlikely to be related to study treatment and it was unknown whether the patient took any dose(s) of study drug because he was not observed taking his first dose in the study clinic and study drugs were not recovered.

Few SAEs were reported in the FISSION, POSITRON, and FUSION studies (≤ 4% of patients in any treatment group). The incidence of SAEs was similar between 12 and 16 weeks of SOF+RBV treatment (4% [22 of 566 patients] and 3% [3 of 98 patients], respectively). No individual SAE occurred in more than 1% of patients in the SOF+RBV treatment groups. Hepatocellular carcinoma (3 patients) and pyrexia and cellulitis (2 patients each) were the only SAEs reported in more than one patient during SOF+RBV treatment. The reporting of hepatocellular carcinoma was not unexpected given that hepatocellular carcinoma is a complication of cirrhosis {17257}, {23851}. Of the three patients with SAEs of hepatocellular carcinoma, two patients had cirrhosis at screening; the third patient was noted to have a cirrhotic liver configuration during evaluation for the malignancy. There was no

apparent clustering of SAEs observed within specific system organ classes and no apparent trend in the types of events reported or onset time observed. Two patients had three treatment-related SAEs during SOF+RBV treatment for 12 weeks: one patient with anemia on Day 20, and one patient with peripheral edema and eczema on posttreatment Day 28. In the SOF+RBV 16 week group, no individual SAE was reported by more than one patient.

Few patients had SAEs during placebo (3% [2 of 71 patients]) and Peg-IFN+RBV (1% [3 of 243 patients]) treatment; none of these SAEs were considered related to treatment. No individual SAE occurred in more than 1% of patients in these treatment groups.

The lowest rates of discontinuation of SOF+RBV due to AEs were observed during 12 and 16 weeks of SOF+RBV treatment (range, 0% to 2%) (Table 40). In the placebo group, three patients (4%) had an AE that led to discontinuation of the treatment regimen. The Peg-IFN+RBV group had the highest proportion of patients who had an AE that led to discontinuation from Peg-IFN+RBV (11%, 26 patients), compared with all other groups (0% to 4%). In the SOF+RBV groups, there were no AEs leading to discontinuation of SOF+RBV that occurred in more than one patient.

7.2.4. Hematology

Table 42 presents a summary of hematology laboratory abnormalities. Consistent with the expected hemolytic anemia associated with RBV treatment, hemoglobin reductions were observed in all RBV-containing treatment groups {21450}. Despite the higher dose of RBV in the two SOF+RBV groups (1000 or 1200 mg daily) compared with the Peg-IFN+RBV group (800 mg daily), the percentage of patients developing hemoglobin < 10 g/dL during SOF+RBV treatment (9% in the pooled SOF+RBV 12 Week group and 5% in the SOF+RBV 16 Week group) were lower than the percentage of patients in the Peg-IFN+RBV group (14%). Based on the RBV prescribing information, the clinical study protocol recommended RBV dose reduction if hemoglobin decreased to < 10 g/dL and RBV discontinuation if hemoglobin decreased to < 8.5 g/dL {21450}. A total of 1% of patients in the pooled SOF+RBV 12 Week group developed a hemoglobin level < 8.5 g/dL, whereas 2% of patients in the Peg-IFN+RBV group had a hemoglobin level < 8.5 g/dL. One patient receiving SOF+RBV discontinued RBV due to anemia. The rate of transfusion in all SOF+RBV groups was < 1%; three patients across all SOF+RBV treatment groups in the Phase 3 studies required a transfusion.

In studies evaluating RBV monotherapy, hemoglobin reductions were approximately 2 g/dL; this reduction is similar to those observed in the SOF+RBV groups in the FISSION, POSITRON, and FUSION studies {3302}, {23297}. In addition, SOF monotherapy was not associated with any hemoglobin reductions in the Phase 2 ELECTRON study.

In non-interferon-containing treatment groups, no effect on neutrophil or platelet counts was observed. Consistent with the expected bone marrow suppressive effects of Peg-IFN and the hemolytic effects of RBV, decreased neutrophil counts and hemoglobin were commonly observed abnormalities in the Peg-IFN+RBV group. No relevant changes in hematology parameters were observed in the placebo group.

Table 42. FISSION, POSITRON, and FUSION: Summary of Hematology Laboratory Abnormalities

Parameter	FISSION		POSITRON		FUSION		FISSION, POSITRON, FUSION
	SOF+RBV 12 Weeks	Peg-IFN+RBV 24 Weeks	SOF+RBV 12 Weeks	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	Pooled SOF+RBV 12 Weeks
	N = 256 n (%)	N = 243 n (%)	N = 207 n (%)	N = 71 n (%)	N = 103 n (%)	N = 98 n (%)	N = 566 n (%)
	N = 254	N = 242	N = 206	N = 71	N = 103	N = 98	N =563
Hemoglobin							
< 10.0 g/dL	23 (9%)	35 (14%)	15 (7%)	0	11 (11%)	5 (5%)	48 (9%)
< 8.5 g/dL	1 (< 1%)	4 (2%)	2 (< 1%)	0	2 (2%)	0	5 (< 1%)
White Blood Cells							
Grade 3 (1000 to < 1500/mm^3)	0	10 (4%)	0	0	0	0	0
Grade 4 (< 1000/mm^3)	0	1 (< 1%)	0	0	1 (< 1%)	0	1 (<1%)
Neutrophils							
Grade 3 (500 to < 750/mm^3)	0	30 (12%)	0	1 (1%)	0	0	0
Grade 4 (< 500/mm^3)	0	6 (2%)	0	0	1 (< 1%)	0	1 (<1%)
Lymphocytes							
Grade 3 (350 to < 500/mm^3)	0	15 (6%)	1 (< 1%)	0	4 (4%)	0	5 (< 1%)
Grade 4 (< 350/mm^3)	0	12 (5%)	0	0	2 (2%)	0	2 (< 1%)
Platelets							
Grade 3 (25,000 to < 50,000/mm^3)	0	18 (7%)	0	2 (3%)	2 (2%)	0	2 (< 1%)

Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir

7.2.5. Chemistry

Table 42 presents a summary of chemistry laboratory abnormalities. The number of chemistry abnormalities was low across the active treatment groups (range, 0% to 6%). In the SOF+RBV 12 Week and SOF+RBV 16 Week groups, hyperglycemia was the most common Grade 3 laboratory abnormality (range, 2% to 6%). In the placebo group, elevated aspartate aminotransferase (AST) was the most common laboratory abnormality (14%), consistent with untreated chronic HCV infection. Grade 3 laboratory abnormalities of hyperglycemia in the placebo group was reported at a similar incidence to that in the SOF+RBV groups (6% versus 2% to 6%) and reflects the 8% to 16% of patients with diabetes mellitus across the treatment groups. In the Peg-IFN+RBV group, elevated ALT was the most common Grade 3 laboratory abnormality (4%).

Table 43. FISSION, POSITRON, and FUSION: Summary of Chemistry Laboratory Abnormalities

	FISSION		POSITRON		FUSION		FISSION, POSITRON, FUSION
	SOF+RBV 12 Weeks	Peg-IFN+RBV 24 Weeks	SOF+RBV 12 Weeks	Placebo	SOF+RBV 12 Weeks	SOF+RBV 16 Weeks	Pooled SOF+RBV 12 Weeks
Parameter	**N = 256 n (%)**	**N = 243 n (%)**	**N = 207 n (%)**	**N = 71 n (%)**	**N = 103 n (%)**	**N = 98 n (%)**	**N = 566 n (%)**
	N =254	N =242	N = 206	N = 71	N = 103	N = 98	N =563
Alanine Aminotransferase							
Grade 3 (> 5.00 to 10.00 × ULN)	0	9 (4%)	1 (< 1%)	6 (8%)	0	2 (2%)	1 (< 1%)
Aspartate Aminotransferase							
Grade 3 (> 5.00 to 10.00 × ULN)	0	3 (1%)	0	9 (13%)	0	0	0
Grade 4 (> 10.00 × ULN)	0	1 (< 1%)	0	1 (1%)	0	0	0
Creatine Kinase							
Grade 3 (10.0 to < 20.0 × ULN)	3 (1%)	0	N/A	N/A	N/A	N/A	3 (1%) [a]
Grade 4 (≥ 20.0 × ULN)	2 (< 1%)	1 (< 1%)	N/A	N/A	N/A	N/A	2 (< 1%) [a]
Lipase							
Grade 3 (> 3.0 to 5.0 × ULN)	1 (< 1%)	3 (1%)	5 (2%)	1 (1%)	1 (< 1%)	0	7 (1%) [b]
Grade 4 (> 5.0 × ULN)	1 (< 1%)	2 (< 1%)	0	0	1 (< 1%)	0	2 (< 1%) [b]
Glucose (Hyper)							
Grade 3 (> 250 to 500 mg/dL)	4 (2%)	4 (2%)	3 (1%)	4 (6%)	6 (6%)	5 (5%)	13 (2%)
Grade 4 (> 500 mg/dL)	0	0	1 (< 1%)	0	0	0	1 (< 1%)
Total Bilirubin							
Grade 3 (> 2.5 to 5.0 × ULN)	6 (2%)	2 (< 1%)	5 (2%)	0	2 (2%)	2 (2%)	13 (2%)

N/A = not applicable; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; ULN = upper limit of the normal range

a n = 254

b n = 562

Increases in bilirubin have been previously associated with RBV-associated hemolysis {21450}. No patients in any treatment group had Grade 4 hyperbilirubinemia. The incidence of Grade 3 total bilirubin laboratory abnormalities was low in patients in the SOF+RBV 12 Week and 16 Week groups (2% each). In the SOF+RBV groups, no patients with a bilirubin elevation had concomitant elevations in transaminases or clinical symptoms such as jaundice, and no patient interrupted or discontinued treatment due to elevated bilirubin. One percent of patients in the Peg-IFN group and no patients in the placebo group had a Grade 3 total bilirubin laboratory abnormality, respectively.

Increases from baseline in median total bilirubin values were observed in both the pooled SOF+RBV 12 Week group and SOF+RBV 16 Week group, which peaked at Week 1 for the pooled SOF+RBV 12 Week group (change from baseline of 0.4 mg/dL) and Week 2 for the SOF+RBV 16 Week group (change from baseline of 0.4 mg/dL). Subsequently, median total bilirubin values decreased and returned to near-baseline levels by the end of study treatment.

No relevant changes in median total bilirubin were observed in the placebo group. Increases from baseline in median total bilirubin values were observed the Peg-IFN+RBV group (maximal change from baseline of 0.1 mg/dL intermittently during treatment). Subsequently, median total bilirubin values decreased and returned to baseline levels at the end of study treatment visit.

To further assess the contributions of SOF and RBV to treatment-emergent changes in bilirubin, Table 44 presents maximum median changes from baseline for bilirubin and reticulocytes during treatment with SOF monotherapy, SOF with increasing doses of RBV, Peg-IFN+RBV, and SOF+Peg-IFN+RBV.

Table 44. Median Changes from Baseline for Total Bilirubin and Reticulocytes During Sofosbuvir Monotherapy, Sofosbuvir with Increasing Doses of RBV, Peg-IFN+RBV, and SOF+Peg-IFN+RBV

Study	Treatment Regimen	N	Maximum Median Change from Baseline	
			Total Bilirubin (mg/dL)	Reticulocytes ($x10^3$/µl)
ELECTRON	SOF 12 Weeks	10	+0.10	+8
	SOF+RBV 800 mg 12 Weeks	10	+0.25	+103
FISSION, POSITRON, FUSION	Pooled SOF+RBV 1000 or 1200 mg 12 Weeks	566	+0.40	+137
FISSION	Peg-IFN+RBV 800 mg 24 Weeks	243	+0.10	+33
PROTON	placebo+Peg-IFN+RBV 1000 or 1200 mg 48 Weeks	26	+0.40	+84
NEUTRINO	SOF+Peg-IFN+RBV 1000 or 1200 mg 12 Weeks	327	+0.20	+38

Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir

Hyperbilirubinemia observed with SOF+RBV treatment appears to be related to a dose-dependent RBV-associated hemolysis as shown by the FISSION (800 mg) and the NEUTRINO (1000 or 1200 mg) studies. In the Phase 3 studies, hyperbilirubinemia was more common with SOF+RBV compared with Peg-IFN+RBV most likely because of the lower RBV dose in the Peg-IFN+RBV group, and because, in the absence of the bone marrow suppressive effects of Peg-IFN, the occurrence of an increased hemolysis with SOF+RBV leading to more reticulocytosis. SOF is not an inhibitor of transporters that are involved in bilirubin elimination (OAT1B1, OATP1B3, and MRP2) or an inhibitor of the bilirubin metabolizing enzyme UGT1A1.

7.3. Safety of SOF+Peg-IFN+RBV Treatment in Patients with Chronic Genotype 1, 4, 5, or 6 HCV Infection in Phase 3 Registration Studies

Safety analyses for SOF+Peg-IFN+RBV treatment from the primary safety population include the 327 patients who received SOF+Peg-IFN+RBV for 12 weeks in the NEUTRINO study.

7.3.1. Overall Summary

Table 45 summarizes the overall summary for AEs for the NEUTRINO study. Although 95% of patients had at least one AE, only 2% of patients discontinued treatment due to an AE. A total of 48 patients (15%) had a Grade 3 AE. The most frequently reported Grade 3 AEs were neutropenia (7%) and anemia, fatigue, and headache (2% each).

Table 45. NEUTRINO: Overall Summary of Adverse Events

Patients with:	NEUTRINO SOF+Peg-IFN+RBV 12 Weeks (N = 327) n (%)
Any AE	310 (95%)
Grade 3 AE[a]	48 (15%)
Any SAE	4 (1%)
AE Leading to Treatment Discontinuation	5 (2%)
Death	0

AE = adverse event; Peg-IFN = pegylated interferon; RBV = ribavirin; SAE = serious adverse event; SOF = sofosbuvir

a There were no Grade 4 AEs reported in this study.

7.3.2. Common Adverse Events

Table 46 presents a summary of AEs that were reported in at least 15% of patients. The three most commonly reported AEs were fatigue, headache, and nausea. The overall AE profile was similar in frequency and the nature of the AEs was consistent with the expected profile for Peg-IFN+RBV treatment. Based on the prescribing information, the primary toxicity for RBV is hemolytic anemia and the most commonly reported adverse reactions for Peg-IFN include flu-like symptoms (fatigue, pyrexia, myalgia, headache, and rigors), psychiatric reactions (depression, insomnia, irritability, and anxiety), anorexia, nausea and vomiting, neutropenia, diarrhea, arthralgia, injection site reactions, alopecia, and pruritus {24700}, {21450}.

Table 46. NEUTRINO: Adverse Events in at Least 15% of Patients by Preferred Term

Preferred Term	NEUTRINO SOF+Peg-IFN+RBV (N = 327) n (%)
Fatigue	192 (59%)
Headache	118 (36%)
Nausea	112 (34%)
Insomnia	81 (25%)
Anaemia	68 (21%)
Rash	59 (18%)
Decreased Appetite	58 (18%)
Pyrexia	58 (18%)
Chills	54 (17%)
Neutropenia	54 (17%)
Pruritus	54 (17%)
Influenza Like Illness	51 (16%)

Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir

7.3.3. Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

No treatment-emergent deaths were reported in the NEUTRINO study.

Eight SAEs were reported in 4 patients (1%). No trends in SAE type or onset time were observed, and no individual SAE was reported in more than one patient. Four SAEs in 2 patients were considered related to any of the 3 study drugs: anemia and cryoglobulinemia in one patient and leukopenia and pyrexia in the other patient.

Five patients had AEs leading to treatment discontinuation. Anemia was the only AE leading to treatment discontinuation in more than one patient (2 patients). Notably, both of these patients achieved SVR12.

7.3.4. Hematology

Table 47 presents a summary of hematology laboratory abnormalities. Consistent with the expected bone marrow suppressive effects of Peg-IFN and the hemolytic effects of RBV, reductions in neutrophil count and hemoglobin were observed {24700}, {21450}. Based on the RBV prescribing information, the clinical study protocol recommended RBV dose reduction if hemoglobin decreased to < 10 g/dL and RBV dose discontinuation if hemoglobin

decreased to < 8.5 g/dL {21450}. RBV dose reductions occurred in 20% of patients. Two patients (< 1%) discontinued treatment due to anemia, and three patients (< 1%) received blood transfusions for anemia.

In studies evaluating Peg-IFN+RBV therapy, hemoglobin reductions were approximately 3.5 g/dL; this reduction is similar to that observed in the SOF+Peg-IFN+RBV group, suggesting SOF does not increase the hemoglobin reduction observed with Peg-IFN+RBV treatment {24700}.

Based on the Peg-IFN prescribing information, the clinical study protocol recommended Peg-IFN dose reduction if neutrophils counts decreased to < 750/mm^3 {24700}. Decreased neutrophil count resulted in Peg-IFN dose modifications in 16% of patients. One patient discontinued Peg-IFN due to neutropenia.

Table 47. NEUTRINO: Summary of Hematology Laboratory Abnormalities

Parameter	NEUTRINO SOF+Peg-IFN+RBV (N = 327) n (%)
Hemoglobin[a]	
< 10.0 g/dL	74 (23%)
< 8.5 g/dL	8 (2%)
White Blood Cells	
Grade 3 (1000 to < 1500/mm^3)	18 (6%)
Lymphocytes	
Grade 3 (350 to < 500/mm^3)	17 (5%)
Neutrophils	
Grade 3 (500 to < 750/mm^3)	49 (15%)
Grade 4 (< 500/mm^3)	17 (5%)
Platelets	
Grade 3 (25,000 to < 50,000/mm^3)	1 (< 1%)

Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir

7.3.5. Chemistry

Table 48 presents a summary of chemistry laboratory abnormalities. The number of Grade 3 or 4 chemistry abnormalities was low (range, 0% to 3%); increased AST was the most common chemistry abnormality.

Table 48. NEUTRINO: Summary of Chemistry Laboratory Abnormalities

Parameter	NEUTRINO SOF+Peg-IFN+RBV (N = 327) n (%)
Alanine Aminotransferase	
Grade 3 (> 5.00 to 10.00 × ULN)	7 (2%)
Aspartate Aminotransferase	
Grade 3 (> 5.00 to 10.00 × ULN)	9 (3%)
Grade 4 (> 10.00 × ULN)	1 (< 1%)
Creatine Kinase	
Grade 3 (10.0 to < 20.0 × ULN)	2 (< 1%)
Lipase	
Grade 4 (> 5.0 × ULN)	1 (< 1%)
Glucose (Hyper)	
Grade 3 (> 250 to 500 mg/dL)	7 (2%)
Sodium (Hypo)	
Grade 3 (121 to < 125 mEq/L)	1 (< 1%)

Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; ULN = upper limit of the normal range

7.4. Safety of SOF+RBV Treatment in Patients with Chronic HCV Infection Awaiting Liver Transplantation

Preliminary safety data are available for 61 patients with HCV infection and hepatocellular carcinoma awaiting liver transplantation treated with SOF+RBV until the time of transplantation or up to 48 weeks.

As discussed in Section 6.2.8, there is no standard-of-care treatment available for chronic HCV-infected patients awaiting liver transplantation or for those who have received liver transplantation and have had a recurrence of their HCV infection. Infection of the uninfected, transplanted liver is universal and is associated with significant morbidity and mortality {19796}. The rate of accelerated, progressive liver disease and cirrhosis in the setting of immunosuppression in the posttransplantation period is high, with rates of moderate chronic hepatitis as high as 27% after a median of 3 years and the progression to cirrhosis in 8% of patients after a median of approximately 4 years {23819}. This study focused on patients with hepatocellular carcinoma awaiting liver transplantation because their time to liver transplantation is generally less than one year, considerably shorter than patients with end-stage liver disease awaiting transplantation. This shorter duration allowed for a more rapid proof-of-principle of efficacy of SOF+RBV for the prevention of post-transplantation recurrence of HCV infection. The patients enrolled in the Pre-Transplant study had less advanced liver disease (72% and 28% of patients were classified as CPT A and B at baseline, respectively) than the general HCV-infected patient population awaiting liver transplantation.

The following section evaluated the safety of patients by CPT classification in the Pre-Transplant study. In addition, safety data from an ongoing study in patients with more advanced liver disease are provided in Section 7.7.2.

Table 49 presents the exposure overall and by CPT classification. Overall, patients received a median of 21 weeks of SOF+RBV treatment (range, 2 to 42 weeks), with similar mean exposure between patients classified as CPT A and B.

Table 49. Pre-Transplant Study: Exposure to SOF+RBV Treatment Overall and by Childs-Pugh-Turcotte Classification

	Overall	CPT A	CPT B
Duration of Exposure	**SOF+RBV (N = 61) n (%)**	**SOF+RBV (N = 44) n (%)**	**SOF+RBV (N = 17) n (%)**
Mean (SD)	19.9 (10.13)	21.0 (9.51)	17.1 (11.41)
Median	21.0	24.0	13.3
Min, Max	2.3, 42.3	3.3, 37.3	2.3, 42.3
Cumulative Number of Patients Exposed Through:			
Baseline	61 (100%)	44 (100%)	17 (100%)
Week 4	58 (95%)	42 (95%)	16 (94%)
Week 8	52 (85%)	39 (89%)	13 (76%)
Week 12	47 (77%)	36 (82%)	11 (65%)
Week 16	39 (64%)	32 (73%)	7 (41%)
Week 20	32 (52%)	25 (57%)	7 (41%)
Week 24	28 (46%)	23 (52%)	5 (29%)
Week 28	10 (16%)	8 (18%)	2 (12%)
Week 32	9 (15%)	7 (16%)	2 (12%)
Week 36	8 (13%)	6 (14%)	2 (12%)

CPT = Child-Pugh-Turcotte; SD = standard deviation; RBV = ribavirin; SOF = sofosbuvir

Table 50 presents the overall safety summary for patients in the pre-transplantation (treatment) phase of the study overall and by CPT classification. Treatment with SOF+RBV was well tolerated in patients with HCV infection awaiting liver transplantation. As compared with the SOF+RBV safety data in the primary safety population, there were higher rates of Grade 3 or 4 AEs, SAEs, and deaths, which can be attributed to the more advanced stage of liver disease and malignancy in these patients. Two patients died prior to liver transplantation: one due to acute renal failure in the setting of bacterial peritonitis and sepsis and one due to pneumonitis. Both patients had discontinued treatment with SOF+RBV due to these events. Eleven patients experienced at least one SAE, none of which were considered

related to study drug by the investigator. Hepatocellular carcinoma, pyrexia, and obstructive umbilical hernia were the SAEs reported in greater than one patient (2 patients each). The overall AE profile was similar for patients classified as CPT A and B.

Table 50. Pre-Transplant Study: Overall Summary of Adverse Events Overall and by Childs-Pugh-Turcotte Classification

	Overall	CPT A	CPT B
Patients with:	SOF+RBV (N = 61) n (%)	SOF+RBV (N = 44) n (%)	SOF+RBV (N = 17) n (%)
Any AE	55 (90%)	38 (86%)	17 (100%)
Grade 3 or 4 AE	11 (18%)	8 (18%)	3 (18%)
Any SAE	11 (18%)	7 (16%)	4 (23%)
AE Leading to Treatment Discontinuation	2 (3%)	1 (2%)	1 (6%)
Death	2 (3%)	1 (2%)	1 (6%)

AE = adverse event; CPT = Child-Pugh-Turcotte; RBV = ribavirin; SAE = serious adverse event; SOF = sofosbuvir

Table 51 presents a summary of AEs that were reported in at least 15% of patients overall and CPT classification. The most commonly reported AEs were fatigue, anemia, and headache. The AEs such as fatigue, pruritus, and hypoalbuminemia occurred more frequently in patients classified as CPT B than CPT A; however, no difference were observed in the rate of Grade 3 or higher AEs between the groups.

Table 51. Pre-Transplant Study: Adverse Events in at Least 15% of Patients Overall and by Childs-Pugh-Turcotte Classification

	Overall	CPT A	CPT B
Preferred Term	SOF+RBV (N = 61) n (%)	SOF+RBV (N = 44) n (%)	SOF+RBV (N = 17) n (%)
Fatigue	23 (38%)	11 (25%)	12 (71%)
Anaemia	14 (23%)	9 (20%)	5 (29%)
Headache	14 (23%)	8 (18%)	6 (35%)
Nausea	10 (16%)	7 (16%)	3 (18%)
Rash	9 (15%)	8 (18%)	1 (6%)
Pruritus	5 (8%)	2 (5%)	3 (18%)
Hypoalbuminaemia	3 (5%)	0	3 (18%)

CPT = Child-Pugh-Turcotte; RBV = ribavirin; SOF = sofosbuvir

Table 52 and Table 53 presents summary of hematology and chemistry laboratory abnormalities overall and by CPT classification, respectively. Grade 3 and 4 laboratory abnormalities occurred in 34% and 10% of patients, respectively. Hyperbilirubinemia was more common in patients classified as CPT B than CPT A, reflecting the more advanced liver disease in patients with CPT B. No patients discontinued treatment due to these transient increases in bilirubin related to RBV-associated hemolysis.

Table 52. Pre-Transplant Study: Summary of Hematology Laboratory Abnormalities Overall and by Childs-Pugh-Turcotte Classification

	Overall	CPT A	CPT B
Laboratory Parameter	**SOF+RBV (N = 61) n (%)**	**SOF+RBV (N = 44) n (%)**	**SOF+RBV (N = 17) n (%)**
Hemoglobin			
< 10.0 g/dL	18 (30%)	11 (25%)	7 (41%)
< 8.5 g/dL	3 (5%)	1 (2%)	2 (12%)
Neutrophils			
Grade 3 (500 to < 750/mm^3)	1 (2%)	0	1 (6%)
Lymphocytes			
Grade 3 (350 to < 500/mm^3)	3 (5%)	1 (2%)	2 (12%)
Grade 4 (< 350/mm^3)	4 (7%)	2 (5%)	2 (12%)
Platelets			
Grade 3 (25,000 to < 50,000/mm^3)	4 (7%)	2 (5%)	2 (12%)

CPT = Child-Pugh-Turcotte; RBV = ribavirin; SOF = sofosbuvir

Table 53. Pre-Transplant Study: Summary of Chemistry Laboratory Abnormalities Overall and by Childs-Pugh-Turcotte Classification

	Overall	CPT A	CPT B
Laboratory Parameter	**SOF+RBV (N = 61) n (%)**	**SOF+RBV (N = 44) n (%)**	**SOF+RBV (N = 17) n (%)**
Alanine Aminotransferase			
Grade 3 (> 5.00 to 10.00 × ULN)	1 (2%)	1 (2%)	0
Aspartate Aminotransferase			
Grade 3 (> 5.00 to 10.00 × ULN)	1 (2%)	1 (2%)	0
Grade 4 (> 10.00 × ULN)	1 (2%)	1 (2%)	0
Gamma-Glutamyl Transpeptidase			
Grade 3 (> 5.00 to 10.00 × ULN)	1 (2%)	1 (2%)	0
Glucose (Hyper)			
Grade 3 (> 250 to 500 mg/dL)	7 (11%)	4 (9%)	3 (18%)
Glucose (Hypo)			
Grade 3 (30 to < 40 mg/dL)	2 (3%)	1 (2%)	1 (6%)
Sodium (Hypo)			
Grade 3 (121 to 124 mEq/L)	1 (2%)	1 (2%)	0
Total Bilirubin			
Grade 3 (> 2.5 to 5.0 × ULN)	5 (8%)	2 (5%)	3 (18%)
Grade 4 (> 5.0 × ULN)	1 (2%)	0	1 (6%)

CPT = Child-Pugh-Turcotte; RBV = ribavirin; SOF = sofosbuvir; ULN = upper limit of the normal range

Treatment with SOF+RBV was well tolerated for up to 42 weeks in HCV-infected patients with hepatocellular carcinoma awaiting liver transplantation. The overall AE and laboratory profiles were generally similar in patients classified as CPT A and B.

In addition, preliminary safety data was submitted in the 90-day safety update from Study GS-US-334-0125 for nine patients with decompensated cirrhosis and portal hypertension. These safety data are further described in Section 7.7.2. In these ongoing studies, SOF+RBV treatment has been well tolerated in both pre-transplant patients and patients with the decompensated liver disease.

Overall, no unique safety signal has been identified in patients classified as CPT B that would preclude broadening application of the Pre-Transplant study to the general population of HCV-infected patients awaiting liver transplantation.

7.5. Safety for Women and Special Patient Populations

7.5.1. Pregnant Women and Nursing Mothers

The predominant circulating metabolite GS-331007, but not SOF, was excreted in rat milk. It is unknown whether SOF or its metabolites are excreted in human breast milk. No adverse effects were observed in the reproductive and development studies, and the NOAELs were ≥ 10-fold relative to the mean clinical exposure at SOF 400 mg. Pregnant and breastfeeding women were excluded from all clinical studies conducted to date with SOF. No pregnancies were reported in patients receiving SOF in the Phase 3 registration studies.

RBV is a known teratogen and contraindicated during pregnancy {24149}, {21450}. Extreme caution must be taken to avoid pregnancy in female patients and female partners of male patients while receiving a RBV-containing treatment and for at least six months beyond treatment cessation, as per the RBV labeling guidelines.

7.5.2. Gender

Rates of overall AEs were slightly higher in females than males; however, rates of Grade 3 or 4 AEs were generally similar between males and females. Anemia was reported at an approximately two-fold higher incidence in female patients compared with male patients during SOF+RBV and SOF+Peg-IFN+RBV treatment. This difference may be due to the generally lower pre-treatment hemoglobin levels in female patients. Additionally, based on lower median BMIs, women may have had higher overall exposures to RBV from the weight-based RBV dosing in the Phase 3 studies. Importantly, SVR12 rates were not lower in females compared with males, suggesting that higher rates of anemia did not negatively impact response rates.

7.5.3. Elderly Patients

There was no upper age limit across the four Phase 3 registration studies. An analysis of AEs across these studies in 66 patients (5%) aged ≥ 65 years showed no substantial differences in the safety profile compared with 1239 patients < 65 years, with the exception of higher rates of anemia (27% versus 11%). Although the relatively small number of patients aged ≥ 65 years precluded definitive conclusions, treatment with the SOF+RBV and SOF+Peg-IFN+RBV regimens in this subgroup appeared well tolerated with no unique safety findings. In addition, there were no notable differences in SVR rates for patients aged ≥ 65 years compared with patients aged < 65 years.

7.5.4. Patients Receiving Opiate Substitution Therapy

Patients receiving opiate substitution therapy (primarily methadone and buprenorphine) were included in the four Phase 3 SOF clinical studies and represented 6% of the patients (77 of 1305 patients). All treatment regimens were well tolerated in these patients with a safety profile consistent with that of the general population. Although the numbers of patients are

small, the efficacy in patients receiving opiate substitution therapy appeared generally similar to patients not receiving opiate substitution therapy.

7.5.5. Children

The studies of SOF in patients aged < 18 years are being initiated.

7.5.6. Hepatic Impairment

No dose adjustment of SOF is required for patients with mild, moderate, or severe hepatic impairment (CPT Classification A, B, or C).

The safety profile of SOF-containing regimens in patients with compensated cirrhosis was similar to that in patients without cirrhosis. In the 20% of patients in the primary safety population with cirrhosis, SOF was well tolerated, with similar rates of AEs and AEs leading to treatment discontinuation in patients with and without cirrhosis. Rates of Grade 3 and higher AEs and SAEs were higher in patients with cirrhosis in all treatment groups. Although rates of Grade 1 and 2 bilirubin elevations were higher in patients with cirrhosis compared with those patients without cirrhosis, Grade 3 bilirubin elevations were similar, and there were no Grade 4 elevations in any patient. This difference is related to the higher baseline total bilirubin values in patients with cirrhosis compared with those without cirrhosis; the median change in bilirubin during treatment was similar in both groups.

In addition, SOF+RBV was well tolerated in 61 patients with hepatocellular carcinoma awaiting liver transplantation treated for a median of 21 weeks (range, 2 to 42 weeks) to prevent post-transplant HCV re-infection. All of these patients had cirrhosis, and 28% of patients were CPT Classification B. The duration of administration of SOF in patients awaiting liver transplantation should be guided by an assessment of the potential benefits and risks for the individual patient.

7.5.7. Renal Impairment

No dose adjustment of SOF is required for patients with mild or moderate renal impairment. The safety of SOF has not been assessed in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or ESRD requiring hemodialysis.

7.6. Safety in Individual Investigator/Compassionate Use Studies

The SOF Compassionate Use Program provides individual investigators access to SOF (to be dosed with RBV with or without Peg-IFN) for emergency use in patients with HCV infection following liver transplantation who have exhausted all other treatment options. Thirty-one patients in nine countries have participated in the program up to the time of the NDA submission, and 29 patients had received at least one dose of compassionate use treatment as of 15 February 2013. No new safety signals were identified when these very sick individuals were treated with SOF in combination with RBV with or without Peg-IFN.

7.7. Additional Safety Data From the 90-Day Safety Update

Safety data for studies ongoing at the time of the NDA submission through approximately April 2013 were provided in the 90-day safety update on 08 July 2013. This update included data from 20 Gilead-sponsored clinical studies, including studies with patients awaiting liver transplantation, HCV/HIV-co-infected patients, and patients with decompensated liver disease. SOF, in combination with other DAA, was generally safe and well tolerated and no new safety concerns were identified based on these additional data.

7.7.1. Safety Data for SOF+RBV for 24 Weeks

Safety data from the NDA submission and 90-day safety update are available for 165 patients receiving SOF+RBV for 24 weeks in Gilead-sponsored studies and 60 patients receiving SOF+RBV for 24 weeks in the SPARE study.

Table 54 presents an overall summary of AEs in the pooled SOF+RBV 12 Week group from the FISSION, POSITRON, and FUSION studies, SOF+RBV 16 Week group from the FUSION study, and pooled SOF+RBV 24 Week group from the Phase 2 QUANTUM study and Phase 2 GS-US-334-0114 study. Across these studies, the safety profile of SOF+RBV for 24 weeks was similar to that of the pooled SOF+RBV 12 Week group and SOF+RBV 16 Week group in the primary safety population.

Table 54. FISSION, POSITRON, FUSION, QUANTUM, and GS-US-334-0114: Overall Summary of Adverse Events

	FISSION, POSITRON, FUSION	FUSION	QUANTUM, GS-US-334-0114
Patients with:	**Pooled SOF+RBV 12 weeks (N = 566)**	**SOF+RBV 16 weeks (N = 98)**	**Pooled SOF+RBV 24 weeks (N = 165)**
AEs	496 (88%)	86 (88%)	147 (89%)
Grade 3 or 4 AEs	41 (7%)	4 (4%)	13 (8%)
SAEs	22 (4%)	3 (3%)	7 (4%)
AE leading to treatment discontinuation	8 (1%)	0	2 (1%)

AE = adverse event; Peg-IFN = pegylated interferon; RBV = ribavirin; SAE = serious adverse event; SOF = sofosbuvir

7.7.2. Safety Data for Patients with Decompensated Liver Disease

At the time of the 90-day safety update, safety data were provided for an ongoing study evaluating SOF+RBV treatment in patients with decompensated liver disease (Appendix 1). A total of nine patients had been randomized to treatment with SOF+RBV for 48 weeks. The majority of patients (67%) were classified as CPT B, with the remaining patients (33%) classified as CPT A.

The median duration of treatment or observation was 10 weeks. Table 55 presents an overall summary of adverse events. No deaths, Grade 3 or 4 AEs, or AEs leading to treatment discontinuation were reported in either group. Consistent with the expected safety profile of RBV treatment, decreases in hemoglobin and elevations in total bilirubin were observed during treatment.

Table 55. GS-US-334-0125: Overall Summary of Adverse Events

Patients with:	GS-US-334-0125 SOF+RBV 48 Weeks (N = 9) n (%)
Grade 3 or 4 AE	0
Any SAE	0
AE Leading to Treatment Discontinuation	0
Death	0

AE = adverse event; RBV = ribavirin; SAE = serious adverse event; SOF = sofosbuvir

7.8. Conclusions on Safety Experience

Across the SOF clinical program, SOF+Peg-IFN+RBV and SOF+RBV treatment regimens were generally safe and well tolerated.

Across the Phase 3 registration studies, the incidence of AEs leading to permanent discontinuation of treatment was low in all SOF-containing regimens (0% to 1%) and lower than the incidence of AEs leading to discontinuation of treatment in the placebo group in the POSITRON study (4%) and Peg-IFN+RBV group in the FISSION study (11%). In the SOF+RBV groups, there were no AEs leading to discontinuation of SOF+RBV treatment that occurred in more than one patient. In the SOF+Peg-IFN+RBV group, anemia was the only AE leading to treatment discontinuation in more than one patient (2 patients). Notably, both of these patients achieved SVR12.

Across all treatment groups in Phase 3 registration studies, the three most frequently reported AEs were fatigue, headache, and nausea. The incidences of these events was highest in the Peg-IFN-containing groups, which was consistent with the expected safety profile of Peg-IFN+RBV treatment {24700}, {21450}. Other than the expected AEs and laboratory abnormalities associated with RBV, the SOF+RBV treatment groups had a safety profile similar to the placebo group. No AEs beyond those expected due to the safety profile for RBV or Peg-IFN+RBV were identified in the SOF+RBV or SOF+Peg-IFN+RBV groups, respectively.

Across all treatment groups in Phase 3 registration studies, there was one treatment-emergent death and few SAEs (≤ 4% in any treatment group). Hepatocellular carcinoma, pyrexia, and cellulitis were the only SAEs reported in more than one patient during SOF+RBV treatment. Hepatocellular carcinoma is an expected complication of cirrhosis {17638}. Overall, there

was no apparent trend in the types of SAEs reported or onset time observed with SOF+RBV treatment.

The safety profile of SOF-containing regimens in patients with compensated cirrhosis was similar to that in patients without cirrhosis. In the 20% of patients in the primary safety population with cirrhosis, SOF was well tolerated, with similar rates of AEs and AEs leading to treatment discontinuation in patients with and without cirrhosis. Rates of Grade 3 and higher AEs and SAEs were higher in patients with cirrhosis in all treatment groups. Although rates of bilirubin elevations were higher in patients with cirrhosis compared with those patients without cirrhosis, this difference was related to the higher baseline total bilirubin values in patients with cirrhosis compared with those without cirrhosis. Other than higher rates of anemia, no differences in the safety profile of SOF+RBV or SOF-Peg-IFN+RBV treatment were observed for women or elderly patients.

In conclusion, SOF was generally well tolerated in patients with chronic HCV infection, including those with hepatocellular carcinoma awaiting liver transplantation. There was no apparent additive effect of SOF on the reported safety profile of Peg-IFN+RBV or RBV treatment {24700}, {21450}, {12558}, {21760}, {23297}, {23298}.

8. BENEFIT RISK PROFILE

SOF is the first oral HCV-specific nucleotide polymerase inhibitor with potent, broad anti-viral activity and a favorable safety profile that has allowed the successful treatment of patients infected with all HCV genotypes, including several patient populations without current treatment options. SOF represents a significant therapeutic advance for patients with chronic HCV infection in two major ways:

- SOF in combination with RBV is the first all oral therapy for patients with chronic genotype 2 or 3 HCV infection, many of whom previously failed treatment or could not be treated.

- SOF in combination with Peg-IFN+RBV provides a shorter, simpler, and more effective interferon-containing regimen for patients with chronic genotype 1, 4, 5, or 6 HCV infections.

The SOF clinical development program has demonstrated that the SOF-based treatment regimens studied have a favorable benefit-risk profile.

8.1. Benefits of Sofosbuvir Treatment

The benefits of SOF treatment include the following:

- **Favorable clinical pharmacology profile:** SOF is administered as a single, once-daily 400-mg tablet and has few dosing restrictions. It can be taken with or without food, with most other medications, and requires no dose adjustments in most circumstances commonly encountered in clinical practice.

- **High response rates across multiple patient populations with reduced treatment duration:** SOF-based regimens have demonstrated high SVR rates across many patient populations. Patients with genotypes 1, 2, 4, 5, and 6 HCV infection achieved high SVR rates (≥ 86%) in the Phase 3 registration studies. For patients with genotype 3 HCV infection, SVR rates following SOF+RBV treatment are similar to those observed with the standard-of-care, Peg-IFN+RBV, with the added benefits of shorter duration and elimination of interferon. For patients with genotype 2 or 3 HCV infection, the availability of an oral treatment administered for 12 to 16 weeks with improved tolerability will allow treatment of many patients who are ineligible, intolerant, or unwilling to undergo treatment with an interferon-containing regimen, which has traditionally required 24 weeks of therapy. These regimens will provide important new treatment options for patients with genotype 2 or 3 HCV infection who failed to achieve SVR after previous interferon therapy.

- **Minimal risk of viral resistance:** SOF's unique mechanism of action allows it to be administered in all patients with chronic HCV infection across all HCV genotypes, with minimal risk for the emergence of viral resistance and its potential clinical consequences.

- **Favorable safety and tolerability profile with no unique safety signals attributed to SOF:** The AEs and laboratory safety profiles of SOF in combination with RBV or Peg-IFN+RBV are similar to that expected from the drugs with which it is co-administered. Rates of treatment discontinuation and dose reduction with SOF-containing regimens in the clinical development program were lower than those usually observed with the current standard-of-care, Peg-IFN+RBV.

- **Favorable efficacy and safety profiles in special HCV populations:** Emergent data indicate that the efficacy and safety profile across the broad patient population in the Phase 3 registration studies are maintained in those patients with the greatest need, including patients awaiting liver transplantation.

8.2. Risks of Sofosbuvir Treatment

The known risks associated with SOF are those associated with the drugs with which is co-administered, RBV or Peg-IFN+RBV. The risks of SOF treatment include the following:

- **RBV:** RBV is teratogenic and embryocidal and has a warning in its prescribing information stating that pregnancy must be avoided during and for six months after treatment. Hemolytic anemia is the most common adverse event with RBV. Other AEs such as fatigue and insomnia are also commonly associated with RBV. The RBV prescribing information provides guidance for dose reductions required for the management of anemia and other AEs {21450}, {24149}.

- **Peg-IFN:** Peg-IFN has a number of potentially serious side effects and a warning in its prescribing information stating that it may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders {24700}, {24701}. The prescribing information also provides guidance for dose reductions required for the management of hematologic toxicities.

- **Use of SOF in patient populations with limited or no safety and efficacy data:** For a new and highly effective drug such as SOF, there is the potential that it will be used in patient populations with a medical need but for whom there are limited or no safety and efficacy data. In these populations, there is the risk for the occurrence of new or more severe side effects or lack of efficacy. Gilead has ongoing or is initiating studies in patients co-infected with HIV, patients awaiting liver transplantation, patients who are critically ill, patients with significant renal or liver dysfunction, and pediatric patients. Studies to optimize treatment in patients with genotype 3 HCV infection are also ongoing as well as studies for treatment-experienced patients with genotype 1 HCV infection using SOF in combination with the NS5A inhibitor, ledipasvir.

8.3. Conclusions

The availability of SOF in combination with other anti-HCV drugs will provide physicians with a new, safe, and effective treatment option for patients with chronic HCV infection. Benefits of treatment with SOF include high response rates with shorter treatment durations than the previous standard-of-care treatments, little risk of the development of resistance, and an improved or similar safety profile to the currently available therapies. For patients with genotype 2 or 3 HCV infection, including those who failed prior treatment or who are ineligible or intolerant to current therapies, it will be the first time that a treatment option is available.

Overall, the results of the SOF development program support the positive benefit/risk profile for the proposed indication for SOF to be administered in combination with other agents for the treatment of chronic HCV infection in adults (Section 1, Table 1).

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10. APPENDICES

Appendix 1. Overview of Key Ongoing Studies in Sofosbuvir Clinical Program

Study Number	Study Design	Treatment Regimens[a]	Patient Population			
			N[a]	Genotype	Prior HCV Treatment	Cirrhosis Status
GS-US-334-0109	Open-label (patients who have participated in prior Gilead HCV studies)	SOF+RBV for 12 or 24 weeks, SOF+Peg-IFN+RBV for 12 weeks	600	Any genotype	TN, TE	Patients were enrolled regardless of cirrhosis status.
GS-US-334-0114	Phase 2, randomized, open-label (Egyptian adults)	SOF+RBV for 12 or 24 weeks	60	4	TN, TE	Up to 20% of patients may have had cirrhosis.
GS-US-334-0125	Phase 2, randomized, open-label	SOF+RBV for 48 weeks or observation for 24 weeks then SOF+RBV for 48 weeks	50	Any genotype	TN, TE	Patients had cirrhosis and portal hypertension with or without liver decompensation.
GS-US-334-0126	Phase 2, open-label	SOF+RBV[b] for 24 weeks	40	Any genotype	TN, TE	Patients with recurrent chronic HCV post liver transplant and Child-Pugh-Turcotte Score ≤ 7.
GS-US-334-0133 (VALENCE)	Phase 3, randomized, double-blind, placebo- controlled	SOF+RBV for 12 or 24 weeks or placebo for up to 12 weeks	400	2, 3	TN, TE	Up to 20% of patients may have had cirrhosis.
GS-US-334-0123 (PHOTON-1)	Phase 3, open-label, multicenter (patients coinfected with HIV)	SOF+RBV for 12 weeks	230	1, 2, 3	TN, TE	Up to 20% of patients may have had cirrhosis.
GS-US-334-0124 (PHOTON-2)	Phase 3, open-label (patients coinfected with HIV)	SOF+RBV for 12 or 24 weeks	270	1, 2, 3, and 4	TN, TE	Up to 20% of patients may have had cirrhosis.
GS-US-334-0139	Phase 2, open-label, expanded access	SOF+RBV with or without Peg-IFN for 24 weeks	N/A	Any genotype	TN, TE	Patients who have undergone a liver transplant and have aggressive, recurrent HCV infection
GS-US-334-0151 (LONESTAR-2)	Phase 2, open-label	SOF+Peg-IFN+RBV for 12 weeks	50	2, 3	TE	Patients may have had cirrhosis.
GS-US-334-0146	Phase 1, open-label, fixed-sequence, multiple-dose (healthy premenopausal female subjects)	Ortho Tri-Cyclen® Lo once daily on Days 1–84, SOF 400 mg once daily on Days 36–42, and LDV 90 mg once daily on Days 57–70	15	N/A	N/A	N/A

Study Number	Study Design	Treatment Regimens[a]	Patient Population			
			N[a]	Genotype	Prior HCV Treatment	Cirrhosis Status
GS-US-334-0153	Phase 3, randomized, open-label	SOF+RBV for 16 or 24 weeks, SOF+Peg-IFN+RBV for 12 weeks	600	2,3	TN, TE	All patients with genotype 2 HCV infection had cirrhosis; patients with genotype 3 HCV infection may have had cirrhosis.
IN-US-334-0141	N/A	SOF+RBV	N/A	Any genotype	TE	Patients who have undergone a liver transplant and have no other treatment options
IN-US-334-0143	N/A	SOF+Peg-IFN[c]+RBV	N/A	Any genotype	TE	Patients who have undergone a liver transplant and have no other treatment options

N/A = not applicable; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LDV = ledipasvir; Peg-IFN = pegylated interferon; RBV = ribavirin; SOF = sofosbuvir; TE = treatment experienced; TN = treatment naive

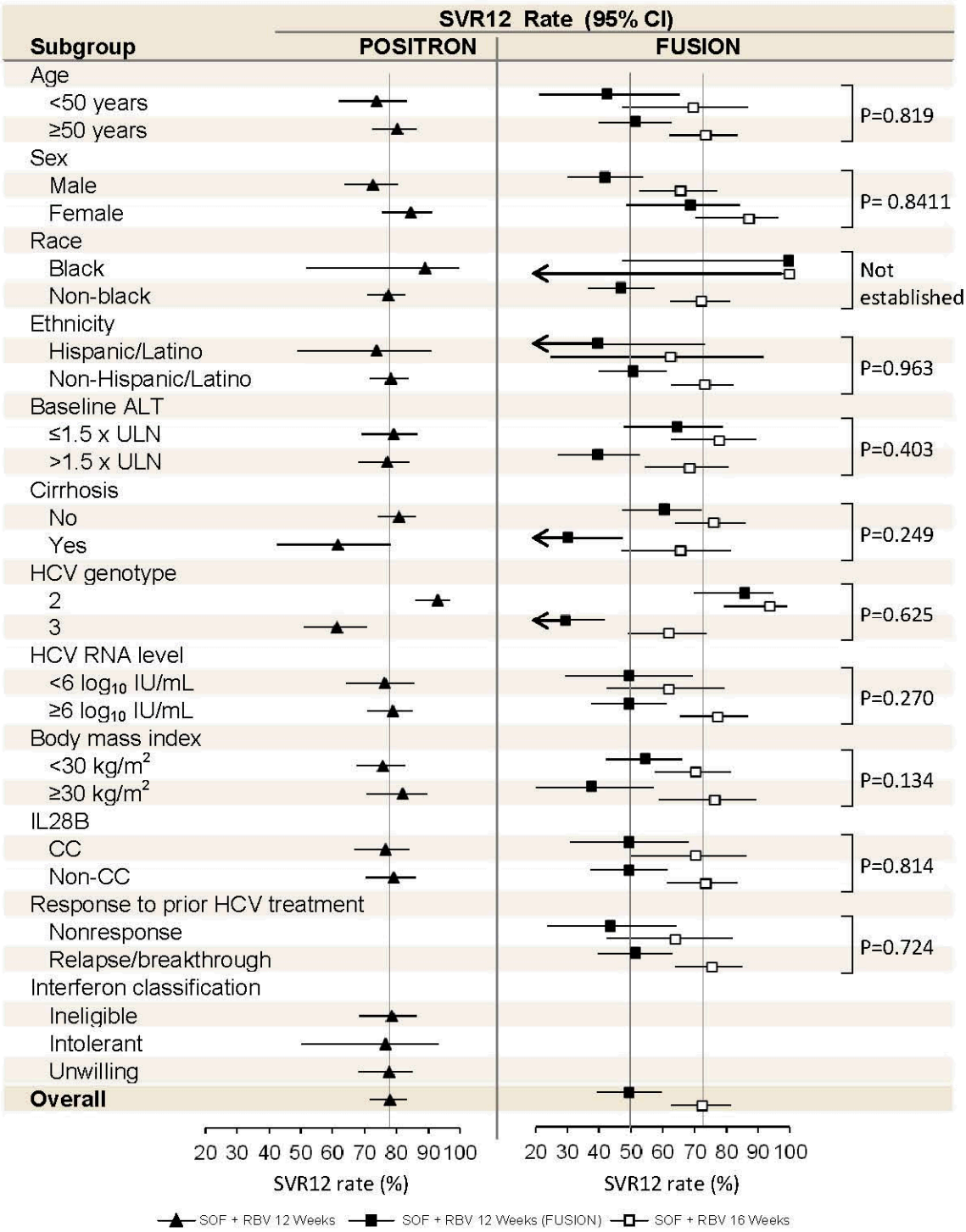
Note: Unless otherwise indicated, the dose of SOF was 400 mg once daily, the dose of RBV was 1000 or 1200 mg daily (for patients who weighed < 75 kg, the dose of RBV was 1000 mg daily in 2 divided doses and for patients who weighed ≥ 75 kg, the RBV dose was 1200 mg daily in 2 divided doses), and the dose of PEG was 180 µg weekly.

a Number of patients planned

b Patients received an initial RBV dose of 400 mg daily (divided dose), which was increased in 200 mg increments to the full weight-based dose (1000 or 1200 mg daily, divided doses) if hemoglobin values were ≥ 12 g/dL.

c Use of Peg-IFN was at the discretion of the investigator based on the specific medical history and ability of the patient to tolerate the side effects of treatment.

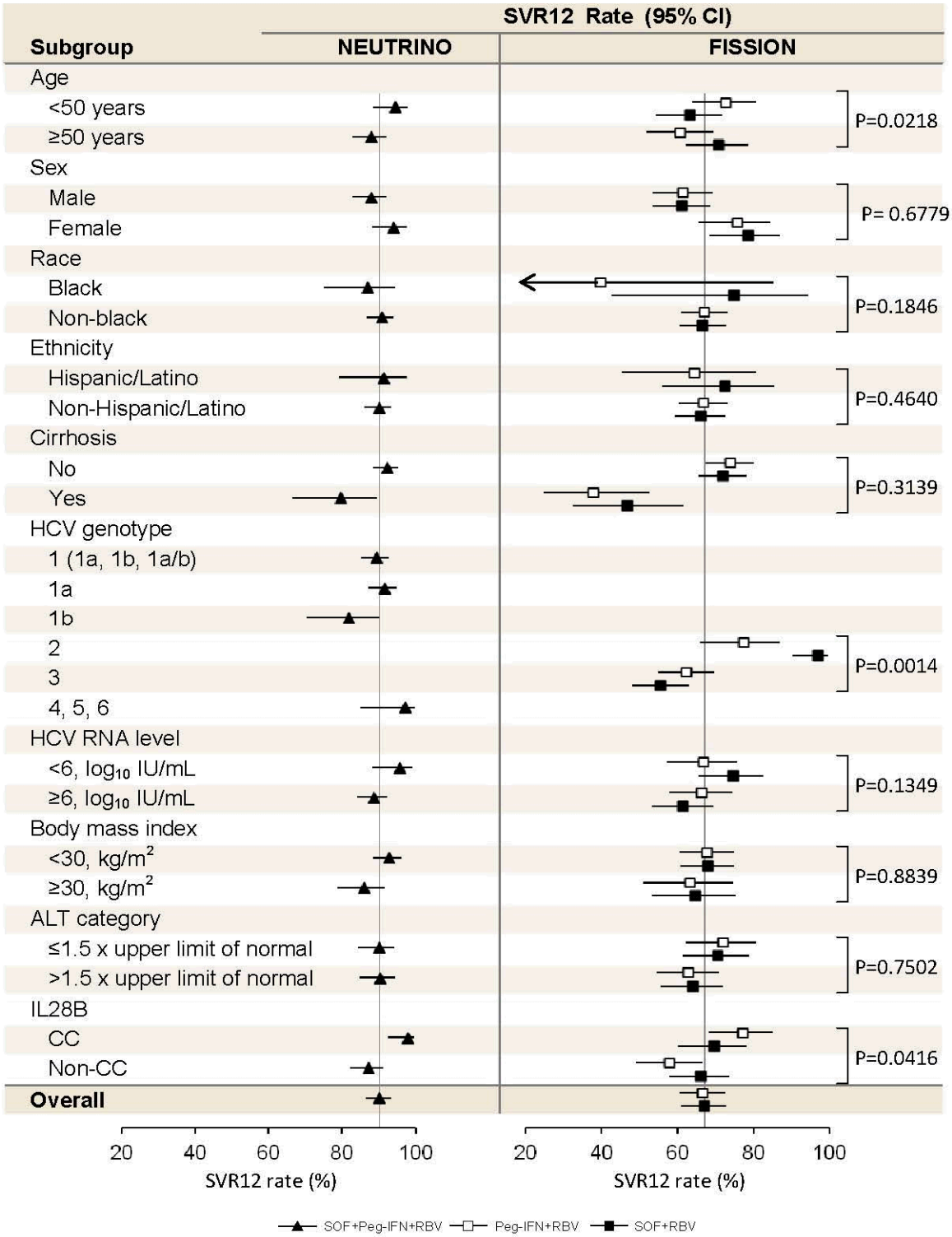
Appendix 2. Forest Plots for the POSITRON and FUSION studies



ALT = alanine aminotransferase; HCV = hepatitis C virus; RNA = ribonucleic acid; SVR12 = sustained virologic response 12 weeks after cessation of study drug; ULN = upper limit of the normal range

Note: P-values represent interactions between treatment groups and subgroups in the FUSION study assessed via logistic regression analysis.

Appendix 3. Forest Plots for the NEUTRINO and FISSION studies



ALT = alanine aminotransferase; HCV = hepatitis C virus; RNA = ribonucleic acid; SVR12 = sustained virologic response 12 weeks after cessation of study drug; ULN = upper limit of the normal range

Note: P-values represent interactions between treatment durations and subgroups in the FISSION study assessed via logistic regression analysis.